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ACTA RADIOLOGICA

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H. Ahlbom

IN MEMORIAM

Cancer research and the combat against cancer suffered a serious loss when on the 19th November, 1952, HUGO AHLBOM, Director of Radiumhemmet, the second holder of the Mimmi Althainz Professorship in Radiotherapy at Karolinska Institutet, died at the early age of 52. The chronic nephritis which was the cause of his death and which during latter years

had diminished his working capacity cannot be ascribed to any form of irradiation injury.

AHLBOM passed his medical examinations with unusually high honours. After a short spell of duty on the surgical side, he was appointed to the junior staff of Radiumhemmet where he remained during 1928 and 1929. He then completed his education by working for eighteen months at the Roentgen Institute of Serafimerlasarettet until he returned to Radiumhemmet to fill various appointments upon the junior and senior staffs until 1944. He obtained his doctorate in 1935 and became 'docent' in 1937. In 1944 he was appointed Director of the Radiotherapy Department of Södersjukhuset, and on the 1st July, 1950, Professor of Radiotherapy and Director of Radiumhemmet, where he was to work for but a short time.

While a junior member of the staff of the Roentgen Institute of Serafimerlasarettet, AHLBOM worked out a method of localizing foreign bodies in the eye, which up to that time, 1931, was considered to be theoretically the best of the methods available.

AHLBOM published five different works concerning cancer of the breast, the most important of which appeared in 1941. In them he surveys 1,815 cases of carcinoma mammae treated during the period from 1921 to 1935 with pre-operative roentgen radiation, operation and post-operative roentgen therapy. The cures achieved are, in Stage I (STEINTHAL) seventy per cent and in Stage II twenty-four per cent. As is known, we now attain a five-year cure in these stages of eighty per cent and forty per cent respectively. In other works, AHLBOM points out the intenability of the old and then classical Steinthal grouping, as it is impossible clinically to decide the nature of palpable glands in the axilla. Twenty-eight per cent of the cases which had been placed in Steinthal's Stage II — that is, clinically with metastases in the axilla, proved not to have cancer of the glands when these were examined microscopically. On the other hand, twenty-two per cent of the cases which were labelled as Stage I — that is, as being clinically without metastases, had metastases in the axilla. Satisfactory classification and statistics of the cases operated upon, he asserts, could only be reached by microscopic examinations of the axillary glands and subsequent grading.

In an early work in 1930, AHLBOM dealt with the value of castration in the treatment of cancer of the breast, a problem which was then the centre of discussion. At that time, he could not prove any real effect from this form of treatment.

The clinical aspects and treatment of parotid tumours formed the subject of AHLBOM's thesis for his doctorate in 1935. Following extensive clinical and histologic investigations, he divided these tumours into benign, semi-malignant and malignant and was able to show that the

tumours which, microscopically, were obviously benign, usually retain their benign character. The malignant growths were malignant from the beginning. The semi-malignant tumours, on the other hand, might become malignant and the introduction of this semi-malignant sub-group has later proved of great importance for the assessment of the prognosis. The technique of treatment, worked out at Radiumhemmet, consists of pre-operative teleradium therapy followed, when the reaction has subsided, by operation on the lines suggested by HYBBINETTE with implantation of radium into the cavity of the wound. The results of this technique of treatment have proved very good as about ninety-five per cent of cures have been obtained in the benign and semi-malignant cases. In the malignant tumours, a five-year cure has been attained by means of radio-surgical treatment in forty per cent of operable cases, and by radiologic treatment alone in twenty-three per cent of cases mainly inoperable.

After AHLBOM was transferred to Södersjukhuset in 1944, he prepared the material from Radiumhemmet of malignant tumours of the testis, 119 cases in all, of which 65 were seminomata, 44 adenomacarcinomata and malignant mixed tumours and 10 unspecified sarcoma-like tumours. Tumours of the testis mainly appear in young individuals and AHLBOM proved that trauma here has no significance although the undescended testis plays an important rôle. He carried out extensive investigations on prolan secretion which was at that time considered to influence the prognosis. He showed, however, that prolan secretion had no significance in the assessment of the prognosis although on the other hand the sedimentation rate in these otherwise young healthy individuals afforded a reliable guide as to the outcome. Treatment consisted of a combination of pre-operative therapy and operation. A five-year cure was effected in sixty-five per cent of cases of seminomata and thirty-five per cent of cases of carcinomata and malignant mixed tumours while the unspecified sarcoma-like tumours presented a considerably worse prognosis with the early appearance of generalized metastases.

In addition to the thesis for his doctorate, AHLBOM's works on the predisposing factors of cancer of the upper digestive and respiratory tracts are of the greatest importance. As early as the nineteen-twenties a peculiar and characteristic atrophy of the mucous membrane of the mouth, especially in women from the North of Sweden under treatment for cancer of the mouth and throat, was observed at Radiumhemmet. In order that this disease phase might be investigated a section of these cases were, on the initiative of FORSSELL, referred to JACOBÆUS at the Medical Department of Serafimerlasarettet. Little light was, however, gained from these examinations. It is AHLBOM who must be praised for having associated the changes in the mucous membrane directly with cancer. WALDENSTRÖM's basic investigations on the diminished iron content in the serum linked

with the associated complexity of symptoms, assisted in clarifying the disease picture. AHLBOM accepted the term 'sideropenia' introduced by WALDENSTRÖM.

In a book, 'Prädisponierende Faktoren für Plattenepithelkarzinom in Mund, Hals und Speiseröhre', published in 1937, AHLBOM collects the experiences he has gained. He points out the strange fact that squamous-cell carcinoma in Sweden affects a proportionally higher percentage of women than men, compared with other countries. Of the patients in Sweden with cancer of the tongue, forty per cent are women, while in Holland, France, Switzerland and U. S. A. the figures vary from three to fifteen per cent. For cancer of other parts of the mouth, the percentage for Sweden reaches forty and for other countries is only about twelve. In cases of cancer of the larynx, in Sweden fifteen per cent are women, in other countries not more than five per cent; in cancer of the oesophagus the comparable figures are forty per cent and twenty per cent respectively. As for cancer of the hypopharynx situated in the posterior cricoid region, and what is known as low hypopharyngeal cancer, AHLBOM finds that ninety per cent of the cases are women and only ten per cent men. It is remarkable that it has only been possible to prove the presence of sideropenia in one per cent of men suffering from cancer of the upper respiratory and digestive tracts.

AHLBOM stresses that most cases of sideropenia are not diagnosed early as investigators concern themselves mainly with the signs of anaemia and do not pay sufficient attention to the history, especially as regards difficulty in swallowing. These difficulties commence as early as childhood and are not recalled spontaneously by the patient which makes it essential that the examiner should enquire into them. AHLBOM points out that in a great number of cases of sideropenia even without manifest signs of cancer, a high-grade atrophy may be noticed in the postcricoid region. The evidence produced by KJELLBERG of the almost constant phenomenon of changes, radiologically demonstrable, in the mucous membrane in this situation, further confirms AHLBOM's conception. Finally, AHLBOM indicates the necessity of spreading knowledge among examiners regarding the relationship of sideropenia to cancer, of prophylaxis by improvement in the living conditions of the women and of careful and repeated examinations once that sideropenia has been established.

The irradiation of this type of growth involves very considerable difficulties owing to the mucous membrane being chronically changed by greatly reduced capacity of reaction brought about by poor conditions of nutrition and resorption. By the technique worked out at Radiumhemmet however, the results have gradually increased from a five-year cure of four per cent to the present fifteen per cent. In connection with this work, AHLBOM also mentions other predisposing factors, previously

recognized, such as tobacco in cancer of the lip and certain other parts of the mouth and alcohol in cancer of the oesophagus. As a great number of cases have been collected at Radiumhemmet over the course of years, AHLBOM has been able to verify statistically the importance of these extrinsic influences on the origin of cancer.

AHLBOM's work on the pre-cancerous changes in the upper respiratory and digestive tracts has with reason attracted considerable attention in the literature. In countries in which the presence of sideropenia had passed unnoticed, many instances of the disease have been found; this is especially so in countries with living conditions similar to those in Sweden *i. e.*, Canada, certain parts of Scotland, and Finland. A few months ago, AHLBOM had the great honour of receiving from the United States a research contribution for the continuance of his investigations.

AHLBOM has also published the results of the teleradium treatment of endolaryngeal cancer at Radiumhemmet. In early tumours of the vocal cords, teleradium produces the same cure rates as operation although the power of speech remains unimpaired. In more advanced cases, he advises hemi- or complete extirpation of the larynx combined with postoperative teleradium treatment.

After his transfer to Södersjukhuset in 1944, AHLBOM developed extensive interests in organizing and mainly occupied himself in working out methods of roentgen treatment in inflammatory conditions.

In 1951, AHLBOM was elected by the Swedish Society of Medical Radiology as one of its representatives on the Editorial Board of Acta Radiologica. In this capacity he assumed the onerous task of advising the editor on questions of therapy and radiobiology. AHLBOM bestowed great interest on this activity. As he was extremely well-read and possessed gifted talent as well as good judgment, his work for Acta Radiologica and its staff was of very great value. Acta Radiologica has suffered a very severe loss in his untimely death.

AHLBOM displayed a most distinguished power of description both in the spoken and written word. He always spoke elegantly and without notes and was prominent as a lecturer and teacher. AHLBOM was exceptionally well-appreciated by his colleagues both for his great knowledge and unfailing willingness to give advice. His sterling and charming personality with the ready smile and friendly gaze gained for him many a warm and sincere friend. As a doctor, his work was stamped by thoroughness, precision and a deep interest in his patients.

HUGO AHLBOM's passing is a grievous blow to Swedish radiology and it will not be easy to replace him. His importance for radiotherapy is established.

Elis Berven

FROM THE ROENTGEN DEPARTMENT (DIRECTOR: PROFESSOR FOLKE KNUTSSON) AND THE PAEDIATRIC DEPARTMENT (DIRECTOR: PROFESSOR BO VAHLQUIST), UNIVERSITY HOSPITAL, UPPSALA, SWEDEN

PREVENTION OF UNDUE INTESTINAL GAS IN ABDOMINAL RADIOGRAPHY IN INFANTS

by

A. Gyllenswärd, H. Lodin and *O. Mykland*

Radiograms of infants' abdominal organs are remarkably often severely impaired because the intestinal tract contained large quantities of gas. Not seldom this makes it impossible to delineate the parenchymatic organs and to evaluate urograms.

The stomach as a rule contains varying amounts of air. This air is swallowed together with the food. NELSON, WYATT and others stated, that crying also tends to carry air down into the stomach of the infant. SOVERI showed radiographically that the more swallowing motions a child performs to ingest a given volume of fluid, the more air it will swallow. DOBROVICI came to similar conclusions. Much evidence suggests, however, that crying is associated with the inspiration rather than the swallowing of air; and, as MAGNUSSON demonstrated by experimenting on himself, air may actually be inspired into the stomach when the glottis is closed. In that manner he inflated the stomach with 0.75 litre of air within 3 minutes.

Any uneructated air is transported further through the child's intestinal tract as soon as it comes in contact with the pylorus (see fig. 1). One of the factors which influences this transport is the posture of the infant. SOVERI studied the emptying of the stomach and bowels in the supine child and found that the air had passed through the empty small intestine generally within 1—2 hours. It should be noted, however, that some of the air would probably be absorbed.

Gas in the large bowel is less detrimental to the results of a roentgen examination than gas in the small bowel, although it may be troublesome

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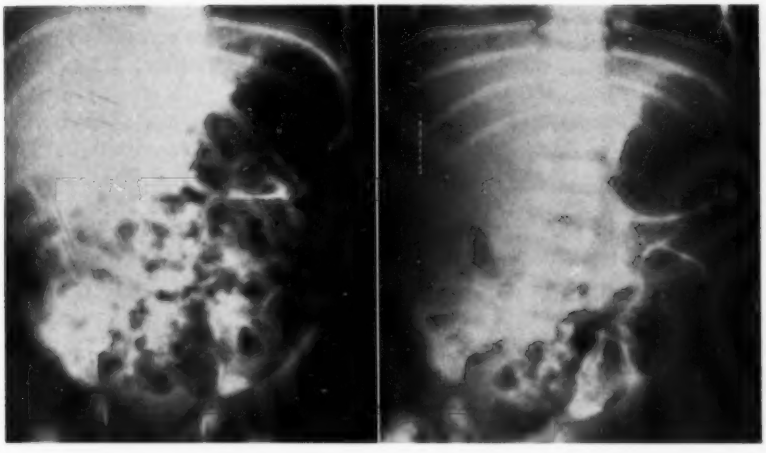

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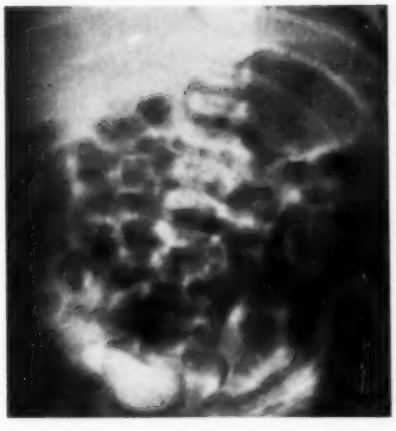


c.

Fig. 1. Urography without preparatory measures in a girl of 2 weeks.

a. Preliminary film, supine, the evening preceding the examination.

b—c. Urography, supine.

if much be present. The gas of the colon is partly composed of air arising from the ileum and partly of gases generated by bacterial activity in the colon. SOVERI has demonstrated that gas usually tends to remain longer in the colon than in other sections of the gastro-intestinal tract, but variable bacterial activity makes it difficult to estimate the differences with any degree of precision. In our experience, however, generated gas is of secondary importance in infants.

For good results in a roentgen examination, gas in the stomach should be prevented from reaching the pylorus during the preceding few hours, and here the child's position is of paramount importance. MAGNUSSON & ENGSTRÖM showed that much less air passes through the pylorus when the child is lying on its right side than on its left. They added that the small bowel usually contains small amounts of gas when the stomach is very distended, the distension signifying that the stomach cannot readily empty. Similarly, WYATT recommended the following three positions: 1. erect, 2. prone with the head slightly raised, and 3. right decubitus. He stressed that the child should not be laid on its back or left side even for a moment and that particular care should be taken during meals, change of clothing, transport, injection of contrast medium and while the actual roentgen examination is carried out. If possible he preferred to examine the children in the erect position.

TROELL has shown that inhalation of pure oxygen affects the partial pressure in the small bowel so that proportionately more nitrogen is absorbed which, in turn, reduces the amount of gas.

ENGEL and SCHALL suggested that wood charcoal should be used to remove gases from the colon; it might be given by mouth or in an enema. MÖLLER doubted this, pointing out that moist charcoal will absorb no gas, and GOODMAN and GILMAN considered that absorbents are incapable of reducing the gas content of a dilated large intestine.

In both children and adults an evacuation enema is a good means of producing a colon free from gas for roentgen examinations. But the method is perhaps less satisfactory in infants; effective emptying can hardly be performed without pressure great enough to cause crying. WYATT pointed out that enemata often produce more gas in an infant's colon than they expel.

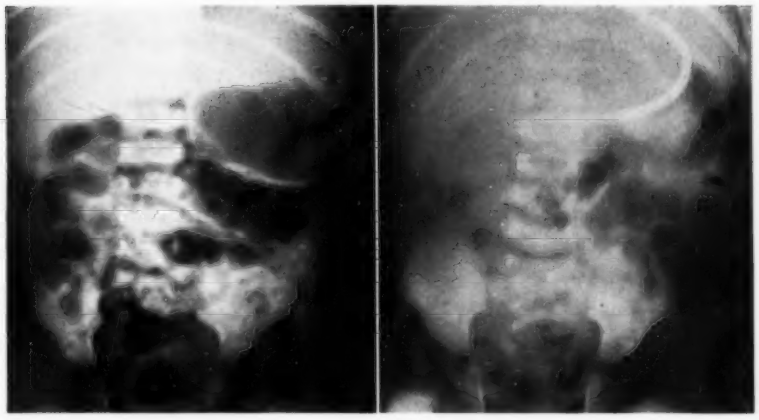
Drugs which stimulate colonic motility have, as evacuation enemata, been widely used as adjuncts to roentgen examinations, and it would appear that suitable laxatives ought to produce satisfactory results in infants as well.

The Authors' Investigations

Our aim was to find a reasonable simple method of preventing intestinal gases, and in so doing we not only tested the effectiveness and practical use of other author's findings but also tried new techniques.

The investigations involved some fifty children between 1 and 14 months of age.

Our first step was to estimate the time it took for air to escape from the stomach when the children were sleeping normally. For this purpose a number of children were radiographed several times during their night's



a. b.

c.

Fig. 2. The same child as in fig. 1 with a tube passed into the stomach from the evening before the examination until the end of the procedure.

a. Preliminary film, supine, the evening before the examination.

b—c. Urography, supine. Note the insignificant amount of gas in the intestines before the examination and the slight increase following it.

sleep. They were lying on their backs and not awakened. It appeared that air escaped fairly quickly from the stomach, but the colon and small intestine still contained much gas after seven hours' sleep.

In order to make the stomach gas escape by way of the mouth instead of the intestines, a tube with multiple vents was passed into the stomach. The free end of the tube was sealed by a water trap and the escaping air collected in a rubber balloon. The children were examined after a night's sleep on their backs. Some air proved to escape by way of the tube, but a considerable amount also entered the intestines (see fig. 2).

When the subjects had been lying on the right side instead of the back, almost gas free small bowels with more air in the balloon often resulted; on other occasions the result was less satisfactory. To get rid of gases of the colon a rectal tube was passed at the same time. In some children almost all the gas escaped from the colon, in others violent tenesmus developed and gave rise to restlessness and worse results than without a rectal tube. Charcoal by both the oral and the rectal route was ineffective. This also applied to an increased oxygen content in the inspired air throughout the night.

Since it was suspected that crying made the children draw in or swallow air alongside the tube, attempts were made to block the oesophagus with a Foley's catheter. Approximately the same amount of air was then collected in the balloon; after $3^1/_2$ hours most of the gas had escaped from the small bowel and some from the colon. The technique was nevertheless unsuitable because so much mucus was secreted in the oesophagus that there was a real danger of its being inspirated. However, the result confirmed our view that in infants gas generated in the intestines is of negligible importance compared to that entering by way of the mouth and stomach.

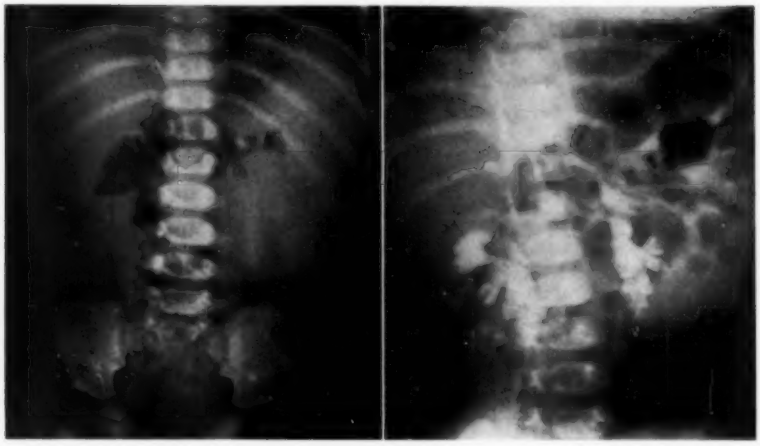
Although these experiments had thus produced certain results, they were not uniformly effective and rather troublesome for the children. We therefore took up the matter of the effect of the child's position on the passage of gas. To judge from the literature and our own experiments it appeared that a prone position the night before the examination should produce the best results, particularly as it is easier to keep the children in such a position than on the right side. A few trials had encouraging results with regard to gas in the stomach and small bowel, but the colon usually still contained a fair amount of gas in the morning. This difficulty was attacked in two ways. Firstly the last two or three meals on the day before the examination were made more viscous by adding 1—2 per cent of Nestargel (Nestlé; dehydrated carob seed cellulose which swells very considerably in water), with the idea that less air would be swallowed with the food and the air still swallowed would pass down through the pylorus less easily; and secondly, the ordinary milk mixture or other food was replaced by a 5 per cent solution of dextrose, in order to inhibit the production of gas in the colon. As an adjuntive measure 1 g of sodium phosphate was administered in order to increase the intestinal transit time. The evening before the examination 0.01 g per kg body weight of phenobarbital was given and next morning a milk formula (To equal parts of cow's milk and water add 2 per cent by weight of wheat flour and 5 per cent of sugar) with Nestargel.

Having ascertained that all the children when on a normal diet and, without special precautions, had approximately the same amounts of

Fig. 3. Boy, aged 5 months.

a. Evening film without preparatory measures.
b. Morning film without food, supine.
c. Morning exposure after night without food, in prone position.
d. A 5 % glucose solution with 1 % Nestargel given instead of the normal diet during the day preceding the examination and morning before the examination. Sodium phosphate and phenobarbital administered the preceding evening; prone position during night.

gas in the various parts of the gastro-intestinal tract every morning, we carried out abdominal roentgen examinations on six children on three consecutive mornings after various preliminary steps. First an exposure was made in the evening without special measures (fig. 3 a); next morning



a. b.

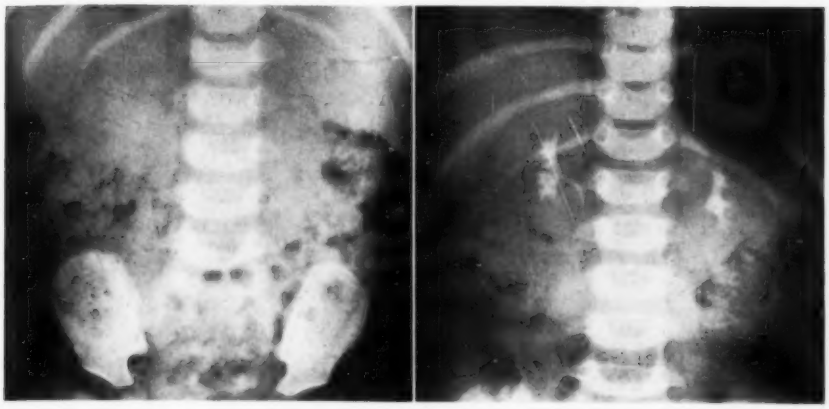
c.

Fig. 4. Urography: boy, aged 6 months, after the same preparatory steps as in fig. 3 d.

a. Preliminary morning film, prone.

b—c. Urography: supine. Note increased intestinal gases.

a further roentgenogram was taken after a night without food in the *dorsal position* (fig. 3 b), the second morning a film was obtained after a night, also without food, in the *prone position* (fig. 3 c) and the third morning the last exposure was made after a night in the *prone position* combined with the special *dietary preparation* outlined above (fig. 3 d). It was found that the first film and the one following dorsal decubitus disclosed large amounts of gas in the small bowel and colon. The film after



a. b.

c.

Fig. 5. a—c. Urography: girl, aged 14 months, in whom the schedule of preparations was carried out in its entirety.

the prone position showed little or no gas in the small bowel and moderate quantities in the colon. The exposure after the prone posture combined with the special diet disclosed if anything less gas in the small bowel, but the colonic gas was still present in moderate amounts. A few of the morning examinations showed quite a considerable amount of gas in the stomach; in these, however, the child had cried.

Another ten children were examined in the prone position after the special preparation and the small bowel contained appreciable amounts of gas in one case only. We now revised our opinion and considered that

the preliminary measures could perhaps be simplified without deterioration of the results. Yet the problem of gas in the colon remained, although as noted this is not, for most examinations, as troublesome as gas in the small bowel. In spite of the fact that, as a rule, we obtained good overall films in the mornings, another problem arose in that the child cried during the examinations causing the small bowel to fill up with gas so quickly that the results were endangered (fig. 4). It was found that this drawback could be eliminated, however, by keeping the child in the prone position throughout the examination and in addition, giving a quick-acting hypnotic, *e. g.* Evipan, in the morning. The colon gas proved partly tractable with 'Relaxit' suppositories (AB. Pharmacia, Sweden) administered before the examination. In contact with moisture these suppositories give off carbon dioxide which collects in the rectal ampulla and stimulates peristalsis of the colon.

Our schedule of preparatory measures was then set out as follows, and has not been changed since.

1. At about 9 p.m. the evening before the examination 0.01 g of phenobarbital per kg body weight and 2 g of sodium phosphate are given in about 40 g of the milk formula.
2. Throughout the night the child lies prone without a pillow.
3. Next morning, half to one hour before the examination, evipan (half of a 0.25 g tablet per 4—7 kg and a whole tablet over this body weight) and half of a 'Relaxit' suppository are administered. This is followed by the milk formula with one per cent Nestargel, fed through a nipple with a large hole or with a spoon, while the child is held upright and immediately replaced on its stomach. The entire examination is carried out with the patient in the prone position. (Any venipuncture should be performed with the child lying on the right side.)

This procedure has proved effective (fig. 5). Among more than thirty children who remained prone during the night and were subjects of over 50 examinations, only two cried and were restless. An occasional child with anomalies of the tongue or jaws could not be placed in the prone position; and older infants sometimes could not be restrained so that they stayed in the prone position. About 30 examinations have so far been carried out in accordance with the above schedule and gas has been found in the small bowel in two cases only; control examinations of the two children without preparatory measures disclosed much more gas. Though not infallible, the procedure produces very satisfactory roentgen films. Although it may suffice in some cases to place the child in the prone position this is not invariably true, and we decided to apply always the full schedule which, after all, is reasonably simple to manage.

If it be desirable to get rid of the gas in the colon of older infants who

are on a mixed diet, it may in occasional cases prove necessary to replace this diet by, for example, the milk formula with 1—2 per cent added Nestargel.

Since the difficulties associated with urography in infants were the main incitement to this investigation, it may be proper to point out that a gas free abdomen is not alone sufficient to ensure success in an urographic examination. Certain features of infantile physiology are often the cause of the films possessing inadequate contrast. The relatively large amounts of fluid ingested by an infant give rise to a high diuresis and a low specific gravity of urine (according to SALOMONSEN 1.002—1.004). A higher contrast concentration may be achieved by restricting the food intake, but is hardly to be recommended as it may disturb the child.

In normal circumstances about 16 per cent of Diodrast is excreted via the glomeruli and the rest via the tubuli, according to BEHRENDT. The same applies to para-amino hippuric acid (PAH). VESTERDAL and TUDVARD studied the inulin and PAH-clearance in children between the ages of 1 and 118 days, and found that both the glomerular and tubular function is low in these age groups. The PAH-clearance, which equals the Diodrast clearance, had attained only half the adult level during the first three months of life. This factor must be compensated by administering a dose of contrast medium considerably in excess of that proportional to the body weight, and WYATT has drawn attention to this point. The contrast medium generally used is Diodrast (Umbradil). If possible it should be given intravenously, but JACOBSSON and GLADNIKOFF reported equivalent results after intramuscular injection with hyaluronidase and xylocaine.

All the five urographic examinations that we have performed in conformity with these recommendations had most gratifying results. Compression was applied and the prone position of the child did not present any difficulties.

SUMMARY

In order to reduce the amount of intestinal gas which is usually troublesome when infants are examined radiographically, the authors have drawn up a schedule of recommended preparations. The child lies on its stomach during the night preceding the examination and this position is maintained throughout the examination; in order to avoid crying, sedatives are given. The composition of the diet is important; it should produce a minimum of gas and yet be viscous; a special milk formula is recommended for this purpose.

ZUSAMMENFASSUNG

Zur Verminderung der Darmgase, die gewöhnlich sehr störend sind, wenn Säuglinge röntgenuntersucht werden sollen, haben die Verf. ein Vorbereitungsschema aufgestellt. Die Kinder werden während der Nacht vor der Röntgenuntersuchung auf den Bauch

gelegt und diese Stellung wird während der Untersuchung beibehalten. Zur Verhinderung des Schreiens werden Sedativa gegeben. Die Zusammensetzung der Kost ist wichtig; sie soll ein Minimum von Gas erzeugen und sehr viskös sein. Zu diesem Zweck wird eine besondere Zusammensetzung der Milch empfohlen.

RÉSUMÉ

Pour diminuer le volume des gaz intestinaux qui d'habitude gênent considérablement les examens radiographiques chez les nourrissons, les auteurs recommandent le schéma de préparation suivant. L'enfant reste couché sur le ventre pendant la nuit qui précède l'examen et pendant tout l'examen ; on lui administre des sédatifs pour éviter qu'il ne pleure; la composition de son régime alimentaire est importante: il doit produire peu de gaz et être très visqueux; une formule spéciale de lait est recommandée à cet effet.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR — AT THE TIME OF THE INVESTIGATION: PROFESSOR Å. ÅKERLUND), KAROLINSKA SJUKHUSET, AND RADIUMHEMMET (DIRECTOR: PROFESSOR H. AHLBOM †), STOCKHOLM, SWEDEN

HYPOPHARYNGEAL CARCINOMA IN SIDEROPENIC DYSPHAGIA

by

Nils Lindvall

Sideropenic dysphagia, previously referred to as the PLUMMER-VINSON's syndrome and in American literature as the PATERSON-BROWN-KELLY syndrome, is particularly well known in Sweden. Its connection with cancer of the upper alimentary canal, more especially of the hypopharynx is also recognized. (Hereafter the disease will be referred to as the P-V syndrome.) Sideropenia is a deficiency disease, and its origin seems to be due to several factors such as heredity changes, unsuitable diet, deficiency in iron, vitamins and so on. According to WALDENSTRÖM's recent investigations, it is not so much the iron as the other contents of the food that are of importance and affect the level of the serum iron. He states that the disease must be regarded as a disturbance of iron metabolism. Epithelial changes resembling those of sideropenia may be manifest at times in the absence of any demonstrable deficiency of either iron or vitamin B. Some authors therefore consider that this disease, like pernicious anaemia, may be caused by a deficiency of either extrinsic or intrinsic factors of which the most significant extrinsic factor is iron.

The most important findings, over and above the oft-occurring hypochromic anaemia, are the various epithelial changes; these are of great diagnostic significance. The most common are rhagades at the corners of the mouth, atrophic changes in the buccal and pharyngeal mucous membranes, dysphagia, changes in the finger-nails, spontaneous fissuring of the finger-tips, and so on. The disease occurs almost exclusively in women.

As far back as 1906, PATERSON reported a case of anaemia with dysphagia. In 1914, PLUMMER gave an account of the same condition. This was again described by PATERSON and KELLY in 1919 and, in 1922,

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VINSON published an article entitled 'Hysterical dysphagia', in which he especially emphasized the fact that anaemia with dysphagia is quite common.

Previously, the P-V syndrome was often described as being anaemia with dysphagia, the anaemia being of the iron-deficiency type. In 1938 WALDENSTRÖM pointed out that he had come across a case of P-V syndrome without anaemia and that later on he discovered three more cases which were all cured by iron therapy. At that time he expounded the hypothesis that the primary factor was not the anaemia, but iron deficiency; and that while sideropenia was a constantly occurring factor in P-V syndrome the anaemia was merely a sign of this lack of iron. Since 1939, then, the syndrome has been called sideropenic dysphagia in accordance with the concept of WALDENSTRÖM and KJELLBERG. Later on, WALDENSTRÖM showed that the serum iron may even be normal despite the presence of epithelial changes. This is especially so in the case of elderly people, in whom both the anaemia and the sideropenia may be cured spontaneously, whilst the lesions on the lips, tongue and in the pharynx persist. Despite this, however, these patients usually react well to iron. Similarly, after treatment, the serum iron may have returned to normal and yet the dysphagia remains because irreversible changes have taken place in the pharynx.

Cases of P-V syndrome accompanied by a megaloblastic, pernicious type of anaemia have also been reported. Some authors are of the opinion that this blood picture is secondary both to the dysphagia and atrophic changes in the gastric mucosa caused by the sideropenia. WALDENSTRÖM has shown that a combination of the iron deficiency and pernicious anaemias is not uncommon. There are numerous cases in which a clinically established iron deficiency anaemia has changed into the pernicious type. In association with this, however, the serum iron increases, though dysphagia may remain. This ought to explain those cases of pernicious anaemia showing valve-like structures that are typically sideropenic.

Before SAVILAHTI reported the results of post-mortem examinations of two typical cases of sideropenic dysphagia in 1946, very little notice was taken of the pathologic changes. Of these, the most characteristic that he found in the hypopharyngeal and oesophageal mucous membranes were degenerative in type. The epithelial cells in the outer and middle layers were seen to contain both unstainable vacuoles in the cytoplasm and degeneration and pyknosis of the nuclei. Cells evidently undergoing frequent mitosis with various sized nuclei and so on were noted in the basal layer. These changes were most marked at the level of the larynx. Local atrophic changes, in addition to those in the mouth, larynx and oesophagus were found in the gastric mucous membrane. Local inflammatory lesions were also present in the oesophagus. There were atrophic

changes in the muscularis together with secondary ingrowths of the connective tissues with a tendency to cause shrinkage and strictures; around the muscle fibers and in the connective tissue a profusion of round cells was noted.

The roentgenologic changes were little observed before KJELLBERG and WALDENSTRÖM in 1939 published their work under the title: "The Roentgenological Diagnosis of Sideropenic Dysphagia." The changes are most often in the upper part of the oesophagus; and, in rare cases are seen as far down as just above the aortic arch. They occur, at times, in the hypopharynx itself. The most frequently occurring changes are fold-like structures projecting in usually from the anterior wall (Fig. 7 a, b). In the more severe forms one may find circular constrictions (Fig. 9 a, b). A very unusual type is that described in 1943 by HOLMGREN, consisting of an elongated constriction in the upper part of the oesophagus (Fig. 5 c, d). LAURELL's original method of demonstrating the changes is used at Karolinska Sjukhuset.

The anatomic basis for these signs is either a spastic condition, the formation of thin membranes, or a shrinkage of the wall. The first two forms may be reversible. When carrying out repeated roentgen examinations of patients, one sometimes finds that the typical changes occurring on various occasions are manifest at different levels, and, occasionally, that they may disappear completely only to recur later on in the same or some other place. They may often be shown during oesophagoscopy.

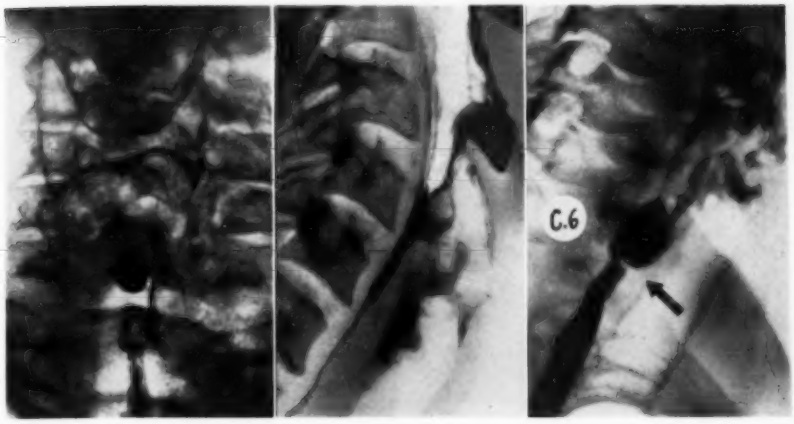
The extent of the roentgenologic changes and the dysphagia do not always run parallel. For instance, in patients who have been afflicted for a number of years, it may be impossible, despite repeated roentgen examinations and a clear clinical picture, to find any deviation from the normal. Patients may on the other hand be found who have been treated and who have become symptomfree and yet the hypopharyngeal-oesophageal changes have not regressed. According to SIMPSON (1939) the reasons for dysphagia may vary. It may be due to: a deficiency of the necessary saliva, spasm, the formation of valve-like structures, superficial ulceration, a generally decreased elasticity, strictures, or malign tumours. According to HURST (1928) the cause may be due to inflammatory and degenerative lesions in Auerbach's plexus.

With regard to the connection between sideropenia and carcinoma, KELLY and PATERSON (1919) and TURNER (1920) found that some of their typical cases of anaemia with dysphagia developed carcinoma of the hypopharynx or the upper part of the oesophagus. This, in their opinion, was scarcely due to mere chance, but rather to the fact that anaemia with dysphagia predisposed the patient to carcinoma. CAMERON (1921) was of the opinion that P-V syndrome and hypopharyngeal carcinoma in

women both possessed the same etiologic factors. In 1933 and 1935 WASSINK in two works showed that women with post-cricoidal carcinoma as well as carcinoma of the upper part of the oesophagus, were as often as not of a certain type or constitution, which, in 1936, he found corresponded with that of hypochromic anaemia or the P-V syndrome. In a material of female patients treated at Radiumhemmet between 1931—1936 for squamous carcinoma of the mouth, larynx or oesophagus, AHLBOM, in 1936, showed that 60 % had had a history of anaemia and dysphagia. When, in 1937, he examined the records of all the women who had been treated at the Radiumhemmet for mesopharyngeal and hypopharyngeal carcinoma during the period 1931—1936, he found that the P-V syndrome was present in 90 % of the cases with postcricoidal carcinoma and carcinoma of the upper part of the oesophagus, and in 50 % of those with carcinoma of the mouth. He considered therefore, that the secondary changes that in time develop in the hypopharyngeal mucous membrane in sideropenia, were precancerous in nature.

Despite the fact that the association of sideropenia with carcinoma has been known for a long time, and that much has been written about it, very little has ever been said about the connection between carcinoma and the valve-like structures observed during oesophagoscopy and roentgen examinations. In 1939 SIMPSON asserted that the finding of a postcricoidal 'web formation' did not signify that a carcinoma would later develop just at that site. KIRCHENBERGER and FLETT (1946) came to the conclusion from their investigations that the so-called 'web formations' in all probability did not undergo malignant degeneration. During the years 1940—1952 a good three hundred cases of hypopharyngeal carcinoma in women with a history of sideropenia were examined at Karolinska Sjukhuset. In ten of these cases, the previous hypopharyngeal roentgen examinations had been so thorough that typical sideropenic changes were detected in the region of the hypopharynx-oesophagus in eight, whereas in the other two they could be precluded. That so few cases were roentgenologically studied is due to the fact (a), that the roentgenologic changes were only recognized for about ten years; (b) that when the patient had a typical picture of sideropenia, treatment was proceeded without any roentgen examination; and (c) that the patients who presented themselves for examination in the roentgen department had, for the most part, been examined only to exclude the possibility of carcinoma. Nevertheless, there are some cases reported in the literature which, during the first hypopharyngoscopic examination, showed typical 'web formations' and, when examined for control purposes some years later, were found to be suffering from carcinoma (JOHNSON 1938, SIMPSON 1939, HUIZINGA 1948, and others).

The eight cases of sideropenic dysphagia with manifest pharyngeal

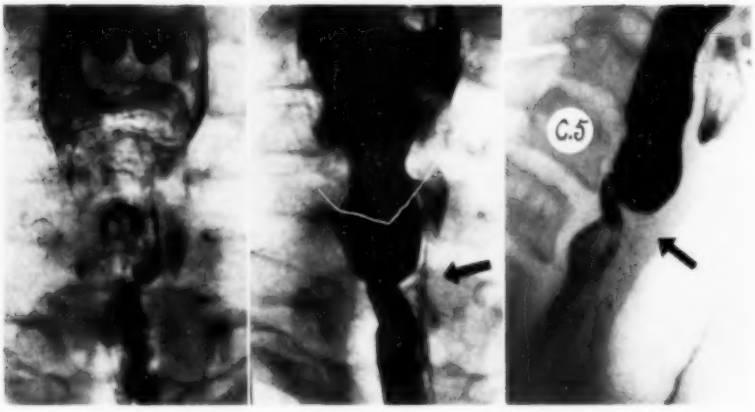


a. b. c.

Fig. 1. Case I. 26. 7. 1934. Normal mucous membrane relief. Sideropenic constriction level with C. 6—7.

changes examined roentgenologically at Karolinska Sjukhuset which, later on, developed carcinoma of the hypopharynx, are representative of the various types of sideropenic changes. One patient showed changes of the HOLMGREN type. Two, in the beginning, had varying valve-like structures that subsequently became permanent; and the remaining five showed constant changes of a valve-like or strictural type right from the first time they were examined.

Case I. (H. B. Journal No. 5570/34.) A woman born 1886, with a typical sideropenic history, had been clinically observed since 1934. At the age of 17 or 18 she was found to have anaemia and was prescribed iron, which she took periodically from that time. At the age of 22 her teeth began to fall out and when she was 28, was fitted with a denture. Her nails had always been defective and she developed fissures at the corners of the mouth on and off for many years. Difficulty in swallowing began when she was 28; to begin with, this was slight although troublesome at times but gradually grew worse. The condition became so accentuated by 1934 that it was hard for her to swallow anything but liquid food. A roentgen examination at the Karlstad Hospital showed a constriction with a somewhat ragged and irregular outline at the level of C. 6—7. She was admitted to Radiumhemmet (Fig. 1). The pharyngeal changes had already been demonstrated in 1919 when an attempt to pump out the stomach was unsuccessful as it was impossible to pass a tube. On admission to Radiumhemmet the blood picture was Hb: 42 %, red corpuscles: 4.2 million. Biopsy showed no neoplastic changes. When examined for follow-up purposes in September 1934, there were no visible changes in either the hypopharynx or oesophagus. She was discharged and her prescription included iron preparations. By October 1934 her swallowing difficulties were so much less as to be scarcely noticeable. She then remained symptom-free until the autumn of 1937 when the difficulties in swallowing re-occurred.



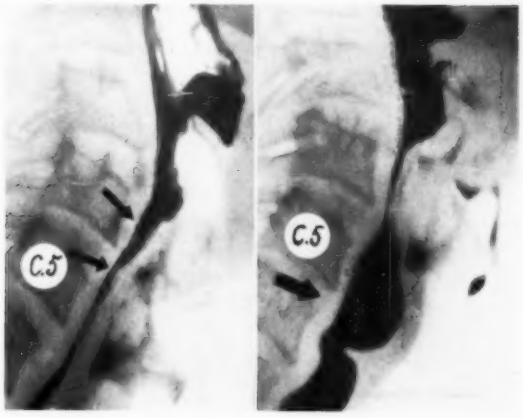
a. b. c.

Fig. 2. Case I. 19. 11. 1943. Normal mucous membrane relief. Sideropenic constriction level with lower margin of C. 5.

As in 1934, the roentgen examination showed that there was a persistent constriction about the level of C. 7. On admission to Radiumhemmet the blood picture was Hb: 62 %, red corpuscles: 4.0 million. She showed considerable improvement after six dilatations, and remained fairly free from symptoms until 1943. Roentgen examination then showed, as previously, a P-V constriction, but no tumour (Fig. 2). R. B. C. — Hb: 73 %, red corpuscles: 4.71 million, serum iron: 0.091 mg %.

In 1946 the patient again became worse and a roentgen examination showed a somewhat increased degree of constriction at the level of C. 7, together with small excrescences on the posterior wall of the hypopharynx just above the stricture (Fig. 3). Oesophagoscopy confirmed the excrescences and biopsy showed that the changes were precancerous; no part of the excised tissue indicated any actual carcinomatous lesion. The excrescences were coagulated superficially but no other treatment was carried out. When re-examined in April 1947 the condition of the patient was found to be somewhat worse. The excrescences could no longer be seen in the roentgenogram, and the posterior wall was smooth and even. At the level of the epiglottis, a slight thickening of the prevertebral soft tissues was observed. As before, biopsy revealed plainly precancerous changes but no signs of actual malignant tissue. On this occasion the blood picture was Hb: 75 %, red corpuscles: 4.41 million, and the serum iron only 0.027 mg %, whereupon an intensive course of iron therapy was initiated which caused the serum iron to increase to 0.320 mg % while her general condition became subjectively good. In September the same year the serum iron was 0.109 mg %. The patient underwent follow-up examinations at regular intervals during 1948 and 1949; she was prescribed iron preparations and the oesophagus was dilated a few times. Clinically, she was fairly free from symptoms; the roentgen changes persisted whilst biopsy still showed the presence of precancerous tissue but there was no evidence of malignancy.

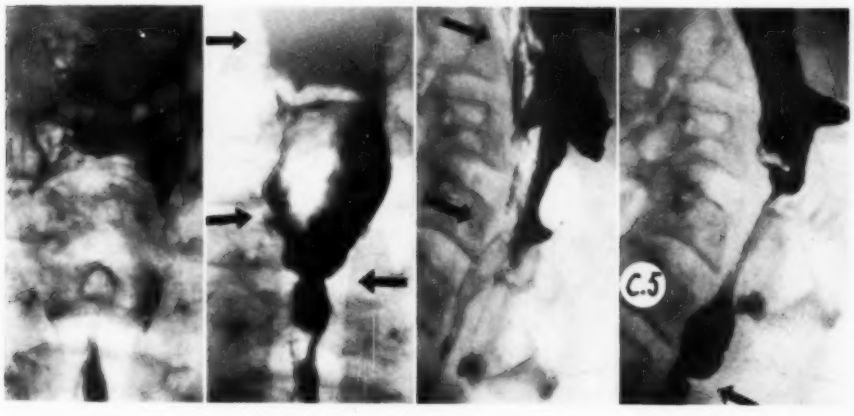
When the patient was examined in the spring of 1950 there was no change in the difficulty in swallowing, but roentgen examination showed that "an irregularity was seen in the relief of the mucosa and in the lateral outline to the right of the hypopharynx ex-



a. b.

Fig. 3. Case I. 19. 10. 1946. Small nodules on the posterior wall of the hypopharynx, proximal to the constriction.

tending from the right vallecula down to the right sinus piriformis". The posterior wall also showed irregularities and as previously, there was a visible valve-like structure. This was separated from the tumour by a free space (Fig. 4). Biopsy showed a small-celled squamous carcinoma growing in cords and with signs of cornification in the form of pearls. After roentgen treatment with tumour doses there was no evidence of carcinoma on biopsy three months later. After a further two months the patient again became worse. However, roentgen examinations and hypopharyngoscopy revealed no recur-



a. b. c. d.

Fig. 4. Case I. 15. 3. 1950. Tumour (Biopsy: carcinoma) to the right of the hypopharynx, extending from the level of the vallecula down to the sinus piriformis. Distal to, and separated from it by a free space, is the sideropenic constriction.

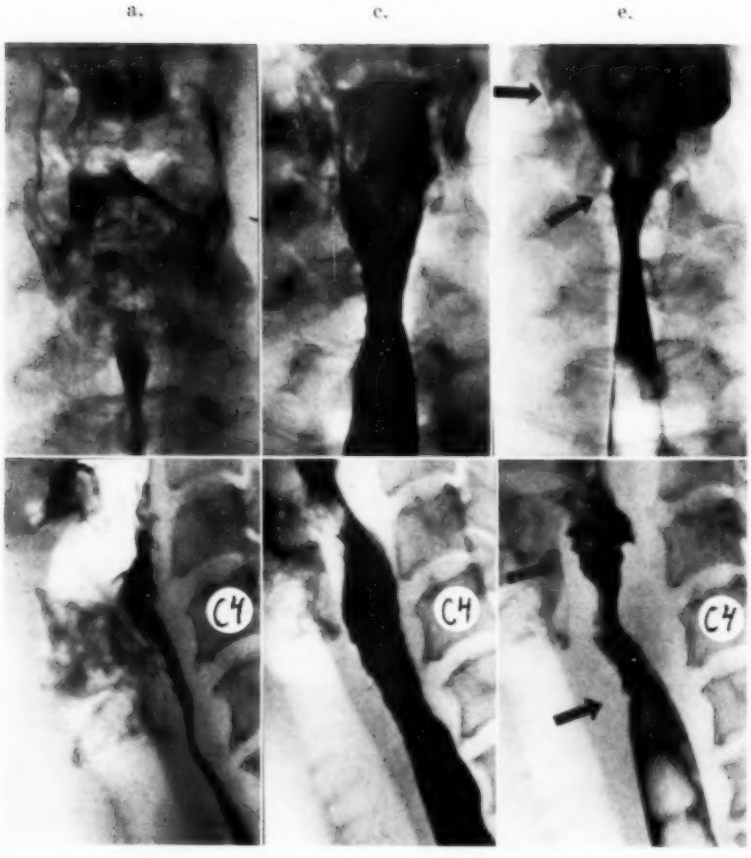


Fig. 5. Case II. 3. 2. 1949. a, b: Normal mucous membrane relief. c, d: Elongated sideropenic constriction.
25. 8. 1950. e, f: Tumour (Biopsy: carcinoma) extending from the arytenoid region a few centimeters distally. The region corresponds to the proximal part of the sideropenic constriction observed in the previous examination.

rence. Serum iron: 0.124 mg %. Considerable improvement after dilatation. In the spring of 1951 valve-like constrictions were seen on roentgen examination. No subsequent signs of recurrence.

Case II. (A. M. F. Journal No. 11841/50. Fig. 5.) A woman, born 1896, with a history of anaemia, persistent rhagades at the corners of the mouth, and frequent blisters

in the mouth for a period of about 25 years. The nails, however, had always been normal. Difficulties in swallowing began at the commencement of 1948. In 1949 she visited the Ear, Nose and Throat Department of Karolinska Sjukhuset. Indirect laryngoscopy revealed normal appearances. When examined roentgenologically the prevertebral soft tissues were found to be of normal thickness but below the arytenoid region, a rather extensive area in the hypopharyngeal-oesophageal region appeared to have a decreased capacity to dilate, similar in type to that sometimes observed in sideropenic dysphagia. No indications of malignancy. Despite treatment, she never really became free from symptoms, and in August 1950, seventeen months later, on indirect hypopharyngoscopy and laryngoscopy, an exophytically growing, papillomatous tumour covering a region twice the size of a haricot bean and extending downwards from the arytenoid region, was found. The Hb was 76 %, red corpuscles: 3.65 million, and serum iron: 0.102 mg %. Roentgen examination on 25. 8. 1950 showed: "Pathologic thickening of the prevertebral soft tissues extending from the arytenoid downwards towards the commencement of the oesophagus. Extending for about 3 cm from the arytenoid down to below the base of the sinus piriformis there is irregularity and rigidity of the mucous membrane." Biopsy: squamous-cell carcinoma. A further examination following roentgen treatment in Febr. 1951, revealed a smooth, atrophic mucous membrane relief with no evidence of recurrence. The prevertebral soft tissues, however, were still thickened.

Case III. (E.V.J. Journal No. 10950/44. Fig. 6.) A woman, born 1883, who, after an operation for a bleeding gastric ulcer at the age of 40, had anaemia of a more or less pronounced form, as well as a feeling of having "something constantly sticking in her throat". At the beginning of 1943, she noticed a resistant mass the size of a walnut, on the left side of the throat towards the inferior part of the larynx, but which never grew any larger. At the same time she also began to experience sensations of pressure in the throat accompanied by certain difficulties in swallowing. She was not hoarse, nor had she lost weight. On admission to Radiumhemmet, there were no signs of sideropenia other than a certain sideropenic appearance. Hb: 62 %, red corpuscles: 4.31 million. Laryngoscopy gave normal findings. The palpable resistant mass appeared to be firmly adherent to the larynx. The roentgen examination report of 22. 6. 1943 read: "Oesophagus and trachea show a slight deviation to the right. At the level of C. 7 and Th. 1 the web formations pathognomonic of the P-V syndrome are seen. Otherwise, there are no changes in the hypopharynx." The clinical diagnosis was P-V syndrome and adenoma of the thyroid. On discharge from Radiumhemmet she was prescribed iron preparations which improved her condition rapidly, with gain in weight, etc. Laryngoscopy on 25. 11. 1943 showed nothing pathologic. In June 1944 on follow-up roentgen examination: "The prevertebral soft tissues at the level of the lower cervical vertebrae show a considerable increase in thickness. A contrast examination of the same region reveals a dilated lumen with a markedly ragged outline. The expansive process reaches from the arytenoid region down to the level of Th. 2. The tumour extends for 8 cm." The findings were confirmed by hypopharyngoscopy. Hb: 63 %, red corpuscles: 4.03 million. Biopsy: "Squamous-cell carcinoma with some cornification." Roentgen treatment. Recurrence.

Case IV. (K. L. S. Journal No. 7613/46. Fig. 7.) A woman, born 1890, who had difficulty in swallowing as long as she could remember. No hereditary history of interest. Since youth had had anaemia for which iron preparations were prescribed. In 1932 she was temporarily afflicted with considerable difficulty in swallowing. Oesophagoscopy revealed nothing pathologic, but the complaint became less marked after the examination and remained so until 1944 when it again became more troublesome. Even when

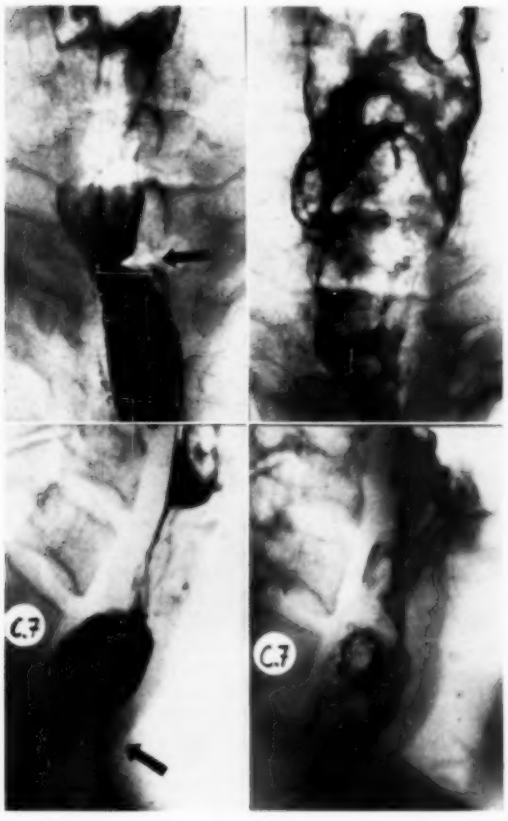
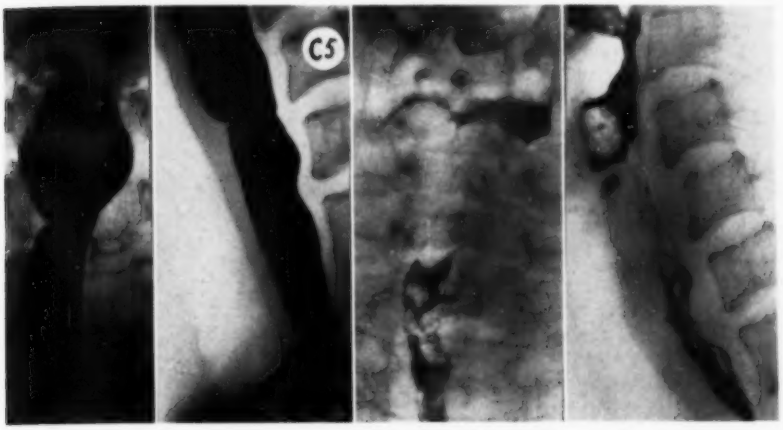


Fig. 6. Case III. 22. 6. 1943. a, b: Typical sideropenic constriction lying level with the lower margin of C. 7.
5. 6. 1944. c, d: Tumour (Biopsy: carcinoma) extending from the arytenoid region down to the middle of Th. 1. The distal boundary of the tumour corresponds to the site of the sideropenic constriction observed in the previous examination.

young she readily developed fissures at the corners of the mouth, whilst the nails had always been very brittle and spoon-shaped. The latter changes, however, receded as she grew older. She lost her teeth at the age of 21—22 years. In 1944 she visited the Medical Outpatient Deparment of Karolinska Sjukhuset. Roentgen examination on 12. 10. 1944 showed: "An entirely normal mucosal relief. Prevertebral soft tissues normal. During maximal dilation of the hypopharynx and oesophagus a typical P-V syndrome fold-like formation is visible at the level of C. 5—6. Otherwise there are no apparent pathologic



a. b. c. d.

Fig. 7. Case IV. 12. 10. 1944. a, b: Typical sideropenic web formation level with the lower margin of C. 5.
18. 5. 1946. c, d: Tumour (Biopsy: carcinoma) extending from the arytenoid region down to the commencement of the oesophagus.

changes." Hb: 75 %, red corpuscles: 3.8 million, serum iron: 0.079 mg %; she was prescribed iron preparations. To a large extent her complaint remained unchanged until the beginning of 1946 when she began to experience a stabbing sensation in the throat accompanied by a burning sensation on swallowing. She consulted a doctor who prescribed large doses of iron and vitamins. As her condition remained unchanged, oesophagoscopy was carried out in April 1946. It revealed a slightly nodular, circular tumour which bled readily and was situated 2 to 3 cm below the upper end of the oesophagus. Biopsy: "Slightly differentiated squamous-cell carcinoma." Roentgen examination on 18. 5. 1946: "The prevertebral soft tissue shadow extending from the level of the arytenoid region down to the commencement of the oesophagus is slightly increased in width. On examination with a contrast medium, considerable irregularity most marked distally is observed over a length of 6.5—7 cm." Hb: 75 %, red corpuscles: 3.99 million, serum iron: 0.120 mg %. After roentgen treatment there was first regression and then recurrence.

Case V. (M. B. E. Journal No. 2698/41. Fig. 8.) A woman, born 1878; no hereditary history of interest. In 1915 during her fourth pregnancy she began to have difficulty in swallowing, which took the form of a feeling of constriction in the pharynx; she found it hard to eat meat. At the corners of the mouth eczema and rhagades that would not heal readily appeared and her nails became brittle and friable. Ten years previously she had lost her teeth. In 1922 she consulted a physician on account of the difficulty in swallowing. It was considered then that "it was just nerves".

In 1941 she began to experience soreness of the tongue, a feeling of dryness of the throat and increased difficulties in swallowing, so that she could take only liquid food. An examination of the gastric juices revealed achylia. In January 1941 she attended the Ear, Nose and Throat Department of Karolinska Sjukhuset, when a typical P-V picture was

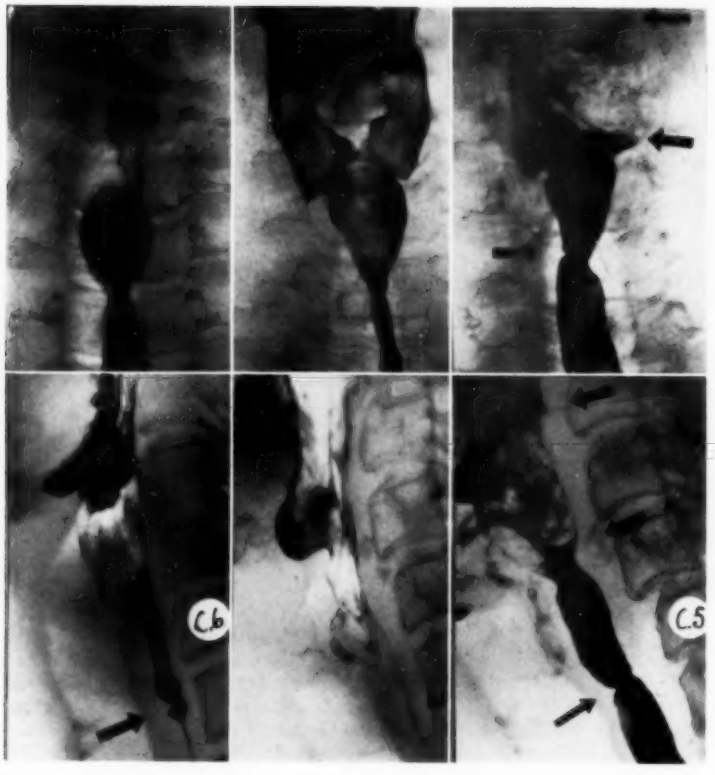


Fig. 8. Case V. 10. 1. 1941. a, b: Circular sideropenic constriction level with C. 6.
2. 9. 1943. c, d: Normal, slightly atrophic mucous membrane relief. Sideropenic constriction as in the previous examination.
8. 7. 1947. e, f: Tumour (Biopsy: carcinoma) to the left of the hypopharynx extending from one finger's breadth above the vallecula down to the bottom of the sinus piriformis. Distal to the tumour, and well separated from it, is the sideropenic constriction.

clinically recognizable. Hb: 98 %, red corpuscles: 4.8 million, serum iron: 0.066 mg %. Roentgen examination on the 10. 1. 1941 showed: "A circular constriction in the pharynx at the level of C. 6, with a slightly fusiform dilation of the hypopharynx above it, on swallowing. Otherwise there is nothing pathologic in the hypopharynx or oesophagus."

In the mesopharynx, to the right of the median line immediately below the uvula, there was a nodular, papillomatous tumour as large as a bean. Biopsy: "Squamous-cell carcinoma of papillomatous structure with some cornification." The tumour was excised and postoperative roentgen treatment together with iron preparations given, following which she showed clinical improvement.

In 1943 swallowing suddenly became impossible. Roentgen examination on 2. 9. 1943 showed: "P-V strictures resembling those seen in the previous examination. Otherwise there is no deviation from the normal picture." She has been subsequently regularly followed-up at Radiumhemmet and the Ear, Nose and Throat Department of Karolinska Sjukhuset. In 1945 and 1946 buccal leukoplakia was recognized and coagulated. In 1946 she was entirely symptom-free, but in 1947 there was a considerable increase in the difficulty in swallowing. Roentgen examination on 8. 7. 1947: "At the level of the entrance to the larynx a neoplasm is seen extending from the left and posterior region and a finger's breadth above the vallecula right down to the bottom of the sinus piriformis. In addition, lying distally to this tumour, the previously reported P-V changes are seen." Hb: 86 %, red corpuscles: 3.5 million, serum iron: 0.121 mg %. Biopsy, 12. 1. 1948: "Squamous-cell carcinoma with cornification." Despite roentgen treatment she grew rapidly worse and died six months later.

Case VI. (A. M. Ö. Journal No. 306/47. Fig. 9.) A woman, born 1889, multipara (4 children) troubled for about 30 years with a "tight throat" and, for the previous 7—8 years, with rhagades at the corners of the mouth. Roentgen examination made 23 years previously revealed no pathologic changes in the hypopharynx or oesophagus. In 1946 she became worse and consulted a physician who sent her to Radiumhemmet. On admission she presented a picture fairly typical of sideropenia with atrophic lips, rhagades at the corners of the mouth, smooth atrophic tongue; she wore upper and lower dentures. Serum iron on 18. 1. 1947 was 0.036 mg %. Roentgen examination carried out on 15. 1. 1947 showed: "The prevertebral soft tissues are of normal thickness. Level with the commencement of the oesophagus is a constriction of the lumen down to about 0.5 cm over a length of approximately 2 cm. Multiple valve-like defects are seen in this constricted region. Nothing to suggest tumour formation and, on swallowing small quantities of contrast medium, the mucous membrane relief appears normal. The roentgen signs are suggestive of the P-V syndrome."

After iron therapy her condition improved subjectively, but when she was examined for control purposes a few months later, widespread leucoplakia was observed in the mouth. Roentgen examination in May 1947 revealed an expansive process at the root of the tongue and sideropenic constrictions resembling those seen in the previous examination. A biopsy showed hyperplastic tissues of the lingual tonsil. The serum iron on this occasion was 0.076 mg %.

Since 1947 she has had follow-up examinations at regular intervals at Radiumhemmet, and the condition has remained largely unchanged. She has received iron as well as vitamins B and C the whole time. The tonsil has received roentgen therapy. Roentgen examination in April 1948 revealed no change in her condition. The serum iron in February 1950 was 0.094 mg %.

During the autumn of 1951 the difficulty in swallowing gradually increased and reached its culminating point in the middle of November. Since then she had been able to swallow only liquid food and had periodic haemorrhages from the throat. Difficulty in breathing and hoarseness had recently bothered her; additionally, she had wasted considerably. On hypopharyngoscopy in November 1951, a large sloughing tumour of cauliflower appearance was discovered filling the whole of the right sinus piriformis and extending to the arytenoid region. The roentgen findings on 21. 11. 1951 were: "The

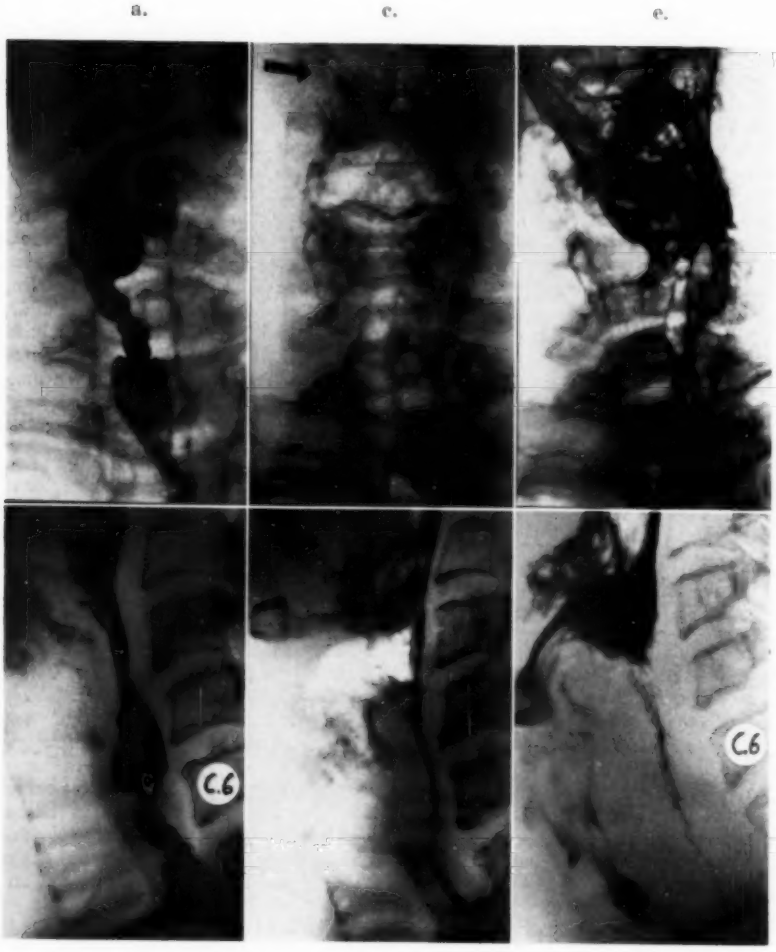


Fig. 9. Case VI. 15. 1. 1947. a, b: Level with C. 6, multiple valve-like structures with considerable constriction of the lumen.
6. 5. 1947. c, d: Hyperplastic lingual tonsil.
21. 11. 1951. e, f: Tumour (Biopsy: carcinoma) extending from the level of the vallecula down to Th. 1.

prevertebral soft tissues are markedly thickened from the level of the vallecula to the jugular notch; maximal thickness: 27 mm. On examination of the area with a contrast medium, a considerable constriction of the lumen, in parts the size of a darning needle, with an irregular outline, was observed. The patient was able to swallow only a very small quantity of dilute contrast medium, most of which ran down into the larynx." Serum iron on 30. 11. 1951: 0.036 mg %. Biopsy showed a squamous-cell carcinoma with some cornification. Tracheotomy and gastrotomy were carried out and roentgen treatment was commenced.

Case VII. (M. K. M. Journal No. 2652/52. Fig. 10.) A woman, born 1878, with typical sideropenia and anaemia, difficulty in swallowing, tongue soreness, rhagades at the corners of the mouth, and brittle nails. The disease began round about 1925 when she had severe metrorrhagia in connection with the menopause. She was treated for difficulty in swallowing at Serafimer Lasarettet in 1925, and the oesophagus was dilated a few times, after which the complaint grew less troublesome. Since then she had been under medical care and had taken iron and liver preparations and in addition, during recent years, vitamin B. In 1940 the Hb was 40 %. In 1946 she was treated in the Medical Department of Karolinska Sjukhuset for sideropenia, 'restless legs', hypertension and chronic polyarthritis. A report of a roentgen examination of the hypopharynx-oesophagus made on 20. 9. 1946, concluded: "No increase in the breadth of the prevertebral soft tissues. When swallowing maximal quantities of a contrast medium, a constriction of the hypopharynx was observed at the level of C. 6. This constriction took the form of a membranal formation and the appearances were typical of the P-V syndrome. The mucous membrane of the hypopharynx was strikingly smooth. No neoplastic changes seen." On this occasion the Hb was 80 %, red corpuscles: 4.3 million and serum iron: 0.073 mg %.

In December 1951, the difficulty in swallowing was accentuated and she commenced to have pains in the throat. At the beginning of April 1952, she visited the Ear, Nose and Throat Department. Roentgen examination on 9. 4. 1952, showed: "Prevertebral soft tissues of normal thickness. On examination with a contrast medium, considerable asymmetry in the arytenoid region, with expansion on the left side, was observed. The left recessus piriformis was not filled, and infiltration was observed to extend almost up to the level of the vallecula. A few valve-like constrictions were seen at the level of C. 6, and there was stenosis of the lumen, which measured between 4 and 5 mm in width." Laryngoscopy revealed a somewhat necrotic tumour as large as the tip of the thumb, situated on the posterior wall of the hypopharynx, immediately opposite to the left arytenoid region and projecting into the lumen. Biopsy: "Squamous-cell carcinoma with some cornification." On 8. 4. 1952 the Hb was 73 %, red corpuscles: 3.8 million, and serum iron: 0.055 mg %. Roentgen treatment was commenced. On 25. 4. 1952 the serum iron was 0.029 mg %.

Case VIII. (S. H. Journal No. 3293/52. Fig. 11.) A woman, born 1889, who, from the age of 18, had been troubled by a feeling of constriction in the throat, anaemia, rhagades at the corners of the mouth, sore tongue and brittle nails. From her 20th year she had had upper and lower dentures. She had been periodically examined, though not during recent years, and given iron preparations. The difficulty in swallowing had alternatively increased and decreased, but never entirely disappeared. From time to time, ever since 1917, she had been examined roentgenologically on account of the difficulty in swallowing. When examined at the Serafimer Lasarettet on 28. 9. 1917, it was found that: "she could swallow a bolus only with great difficulty; this lodged in a retort-shaped recess immediately above the entrance to the larynx, until, after continual swallowing efforts, it passed down behind the larynx in a narrow column and then once more produced a

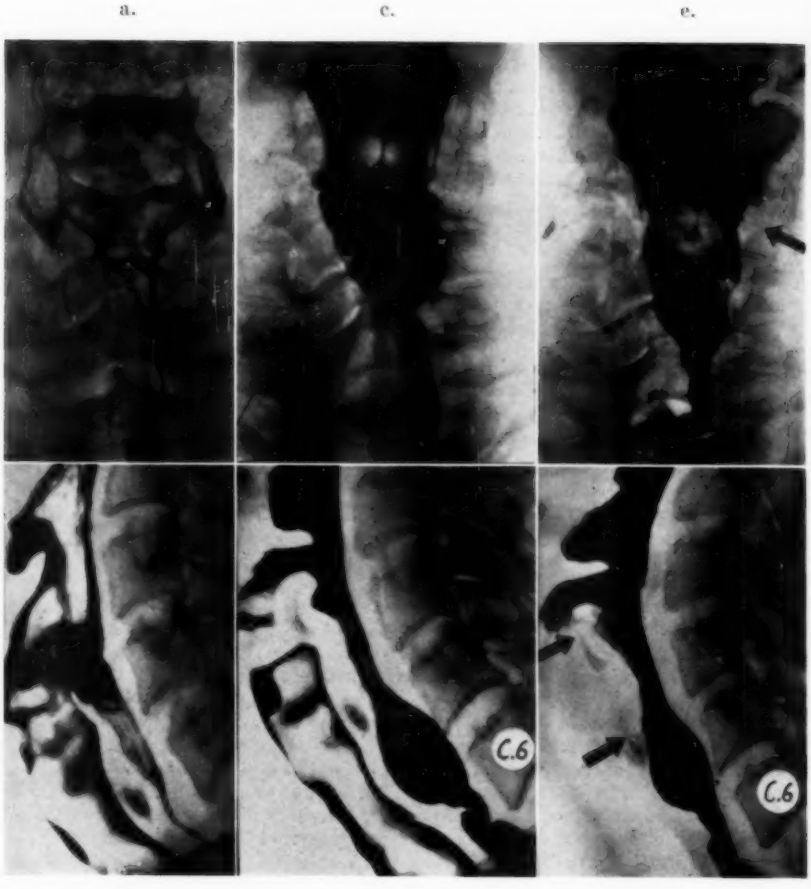


Fig. 10. Case VII. 20. 9. 1946. a, b: Normal mucous membrane relief. c. d: Typical sideropenic constriction level with C. 6.
9. 4. 1952. e, f: Tumour (Biopsy: carcinoma) to the left of the hypopharynx, extending from the vallecula down to the bottom of the sinus piriformis. Distal to, and separated from it by a free space, is the sideropenic constriction.

normal shadow below the laryngeal level." There was no such constriction visible when she was examined in April 1921 or June 1924. In 1941 she was roentgenologically examined at the Åsö Hospital when again a sideropenic constriction was found, on this occasion, at the level of Th. 1.

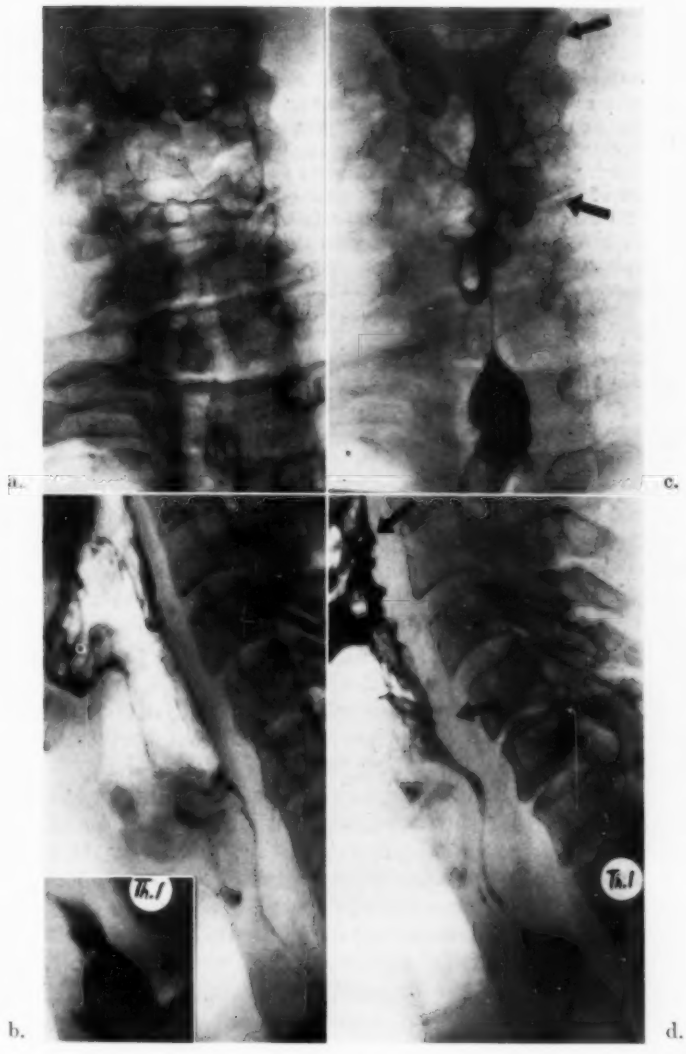


Fig. 11. Case VIII. 8. 5. 1941. a, b: Normal mucous membrane relief. Sideropenic constriction level with Th. 1.

6. 5. 1952. c, d: Tumour (Biopsy: probably carcinoma) extending from the mesopharynx to the arytenoid region. Level with Th. 1, a typical circular sideropenic valve well separated from the tumour.

During the previous few months she became progressively hoarse until finally the difficulty in swallowing became so severe, that she was sent to the Ear, Nose and Throat Department of Karolinska Sjukhuset where a neoplasm of the hypopharynx was found. She was transferred to Radiumhemmet. On admission a rather typical sideropenic appearance was noted together with moderate rhagade formation at the corners of the mouth, a pale complexion and an atrophic buccal mucosa. On 16. 5. 1952 the Hb was 85 %, red corpuscles: 4.9 million, and serum iron: 0.147 mg %. Roentgen examination on 6. 5. 1952 showed: "The prevertebral soft tissues corresponding to the hypopharynx and the lower part of the mesopharynx have an increased thickness with a post-cricoidal thickness of 26 mm; even the epiglottis is considerably thicker than normal. On examination with a contrast medium, an irregular relief of the mucosa is seen prevertebrally in the mesopharynx and hypopharynx and extending down to the level of the arytenoid region. Level with the first thoracic intervertebral disc is a typical sideropenic constriction, above which the lumen isdilated." Hypopharyngoscopy, 17. 5. 1952: "The whole of the posterior wall is coated with a relatively thick layer of fibrin. Inferiorily, a diffuse tumour is seen; it does not extend into the larynx, but the mucous membrane of the larynx is reddish and swollen. The posterior part of the vocal chords are covered with a thick coating of fibrin." Biopsy: "The squamous-cell layer has a general precancerous appearance and a carcinomatous change is strongly suspected." Roentgen treatment.

In four of the eight cases reported above, a carcinomatous growth was situated proximal to the constriction and separated from it by an apparently tumour-free area. In three of the cases the most distal part of the elongated tumour comprised the valval region, and in the eighth case with the atypical elongated sideropenic constriction, the tumour was seen situated within the proximal part of the constriction, that is to say, proximal to its point of maximal size. Of the about 300 female patients examined at Karolinska Sjukhuset during the period 1940—1952 for sideropenia with hypopharyngeal carcinoma, the cases reported above form a very small percentage. In addition to the 10 cases which were roentgenologically examined before the development of the hypopharyngeal carcinoma, films following the swallowing of large quantities of a contrast medium have been obtained prior to roentgen therapy in a further 41 cases in order to show the concomitant presence of sideropenic constrictions in the pharynx. The reason why such examinations were not always carried out was because some of the patients were unable to swallow large quantities of a contrast medium all at once, whereas in other cases it was due to the size of the tumour, and again, when once the case was diagnosed as cancer, one had no desire to cause the patient unnecessary suffering and discomfort by so exhausting an examination. In 34 cases it has been possible to establish the presence of both carcinoma and sideropenic constrictions in the pharynx. HOLMGREN (1939), JOHNSTONE (1946) and WEYDE (1947) have all previously reported their own special cases. In 28 of these 34 cases, the sideropenic constriction was situated below the tumour, either in close proximity to its distal part (14 cases) or sepa-

rated from it by an apparently tumour-free area (14 cases). In 5 of the cases there was a fold-like contraction of the anterior wall corresponding to the distal part of a tumour involving the posterior wall, and in 1 case it was found proximal to the tumour. In 7 cases no sideropenic constrictions were seen; whether or not this was because the tumours had involved that region cannot be definitely decided; in some cases, however, this must have been the case.

In female patients suffering from hypopharyngeal carcinoma and sideropenia, one may thus find, provided it be possible to examine the pharynx fully dilated with a contrast medium, that in addition to the carcinoma there are also in the majority of cases sideropenic valve-like or strictural changes; these, in the vast majority of cases, will be seen to be situated distally to the tumour. We may thus also conclude that as a rule these valve-like and strictural changes, which have great diagnostic value, never will be the point where the malignant degeneration starts. As mentioned above carcinoma may appear non-selectively in the upper alimentary canal.

SUMMARY

After a short summary of the etiology, pathology and typical roentgen findings of sideropenia and its association with carcinoma of the upper alimentary canal, 8 typical cases of sideropenic dysphagia with manifest roentgenologic pharyngeal changes are described together with the follow-up examinations until carcinoma of the hypopharynx developed. A comparison of all the cases of hypopharyngeal carcinoma in women with sideropenia examined at the Roentgen Department of Karolinska Sjukhuset, Stockholm, during the years 1940—1952 shows that, in the majority of cases in which there is a possibility of examining the pharynx fully dilated with a contrast medium, sideropenic valve-like or strictural formations are found. In a preponderant number of cases, these are situated distally to the carcinomatous region. Furthermore, the examinations show that as a rule the constrictions never undergo malignant degeneration.

ZUSAMMENFASSUNG

Nach einer kurzen Übersicht über die Ätiologie, die Pathologie und die typischen Röntgenbefunde der Sideropenie sowie deren Beziehungen zum Karzinom des oberen Teiles des Verdauungskanales beschreibt der Verf. 8 typische Fälle von sideropenischer Dysphagie mit manifesten röntgenologischen Veränderungen im Pharynx sowie Kontrolluntersuchungen bis zur Entstehung eines Carcinoma hypopharyngis. Ein Vergleich aller Fälle von Carcinoma hypopharyngis bei Frauen mit Sideropenie, die während des Zeitraumes 1940—1952 im Röntgeninstitut des Karolinska Sjukhuset untersucht wurden, zeigte, dass man in der Mehrzahl der Fälle, in denen es möglich war, den durch Kontrast voll ausgefüllten Pharynx zu untersuchen, ausser dem Karzinom klappenartige oder strikturierende, sideropenische Bildungen findet und dass diese überwiegend distal vom Karzinom belegen sind. Weiterhin zeigte die Untersuchung, dass diese Verengerungen in der Regel nicht malignisieren.

RÉSUMÉ

L'auteur rappelle brièvement l'étiologie, la clinique et les signes radiologiques typiques de la sidéropénie et de son association avec le cancer des voies digestives supérieures puis présente 8 cas typiques de dysphagie sidéropénique s'accompagnant de modifications radiologiques manifestes du pharynx, ainsi que les examens de contrôle jusqu'à l'apparition de cancer de l'hypopharynx. L'étude comparative de tous les cas de cancer de l'hypopharynx chez des femmes atteintes de sidéropénie et examinées dans le Service de Radiologie de Karolinska Sjukhuset, Stockholm, de 1940 à 1952 montre que dans la majorité des cas où il est possible d'examiner le pharynx complètement dilaté par le produit de contraste, on trouve des images de valvule ou de rétrécissement, et que, le plus souvent, celles-ci sont en situation distale par rapport au cancer. Les examens montrent de plus qu'en général les rétrécissements ne subissent jamais de dégénérescence maligne.

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FROM THE ROENTGEN DEPARTMENT (DIRECTOR AT THE TIME OF INVESTIGATIONS: PROF. Å. ÅKERLUND), KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

CONTRAST LEVELLING IN PROJECTION PRINTING OF REDUCED-SCALE PRINTS

by

Ove Mattsson

The author's method of contrast levelling in printing radiographs, described in 1951, has been particularly extensively used in connection with angiographs. These are mostly made on the larger sizes of film and full-scale copying is a fairly expensive matter owing to the relatively high cost of photographic printing paper. A print of reduced size would usually serve as well, be easier to handle and less liable to damage. It is also probable that no further reduction would be necessary for block making if the print were required for reproduction. Arrows and similar markings are also drawn in more easily and more true to scale on a print approximately of the same size as the final block.

For these reasons it has proved desirable to produce contrast levelled prints of reduced size. The author has been influenced by inquiries from colleagues in countries in which shortages permit but restrictive use of the larger sizes of paper. The consideration of direct transparencies may also be justified. (In this paper the radiograph proper is referred to as a negative, and a film showing inverted tone values as a positive.) In this respect it is relatively easy to produce negative prints from radiographs by means of a small positive — a film or plate. Ordinary positive prints are frequently not very suitable for illustration purposes, and negative prints, similar to the original radiograph, are therefore to be preferred (British and American journals usually demand negative copies for illustration purposes). Tests have been made with various types of paper which directly, without intermediary processing, give prints with the same tone values as the originals. At present these give no acceptable results with roentgen films; the print produced is too contrasty and hard, although the procedure has promises for the future. Photographing a

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paper print on to paper in order to obtain a negative, a method which the author has proved to be possible, often causes such loss of tone values that the intermediary use of plate or film is to be preferred. It is becoming more and more usual for the larger hospitals to employ a copying camera for projection printing and general reproduction work. Furthermore, any type of universal camera with a first class lens may be used for the purpose.

The author's method of contrast levelling in contact printing consists in the use of a print on thin document or ordinary printing paper used as a mask to level the illumination (Acta radiol. 35 (1951), 179). The mask which is wet and therefore more transparent, is laid out on an opal glass plate illuminated from below. The clearer areas of the film correspond to a heavy blackening of the mask. The radiograph is laid on a glass plate above and carefully in register with the mask. In order to eliminate double contours or influence from the paper structure of the mask a distance of about 1 cm (0.7 to 1.4 cm) between it and the film has proved suitable. In making the print, the printing paper is laid against the film and pressed flat by means of a weighted foam-rubber sheet or air-filled pressure pad.

The carrying out of printing with contrast levelling by photographing the roentgen film, placed horizontally and illuminated from behind through the mask, did not give favourable results. Disturbing contour phenomena appeared because the camera registered both film and mask with equal sharpness. But there was also a very marked disagreement of contours, particularly within the peripheral regions of the print. The reason for this is that the bundle of rays collected by a camera lens is conical, and hence, as film and mask are at a distance of approximately 1 cm from each other and are congruent in detail, a marked parallax is produced within the major part of the print area. Theoretically, this parallax may only be eliminated by increasing the lens-film distance to infinity so that the rays are parallel; reproduction photography, however, is usually carried out at distances between 0.5 m and 1 m and for film sizes up to 30 by 40 cm the phenomenon is clearly visible.

Attempts were made to place the mask and film closer together. This somewhat improved the registration, but other disturbing contour phenomena which effaced certain details, appeared. In ordinary printing these defects were successfully eliminated by separating film and mask and thereby assisting the diffusion of light. It now only remained to overcome the parallax contour difference in order to attempt to cause diffusion so that the contour phenomena were eliminated.

In order to achieve this end, the detail contained in the mask should be on a somewhat larger scale than that in the radiograph. All details within the conical bundle of rays reaching the lens will then register with that

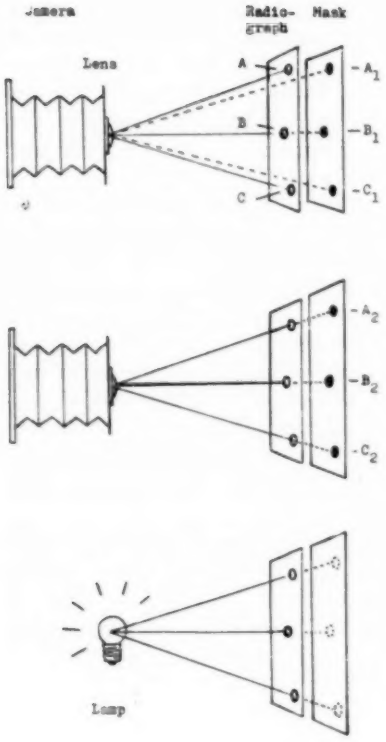

Fig. 1 a—c. Path of rays when a radiograph with contrast levelling mask is photographed. Points on radiograph: A, B and C; corresponding points on mask: A_1, B_1 and C_1 (in Fig. 1 a) and A_2, B_2 and C_2 (in Fig. 1 b). Fig. 1 a: The conditions when film and mask are identical in size; parallactic phenomena appear. A and A_1 each correspond to one ray directed towards the lens. This also applies to C and C_1, while B and B_1 situated on the extension of the longitudinal axis of the lens correspond to the same ray of light. The use of a mask on a suitably enlarged scale — Fig. 1 b — will eliminate the phenomena; all rays against the lens will then pass through corresponding points. Fig. 1 c: The inverted path of rays by which the mask is produced.

in the mask, so that parallax is avoided. Fig. 1 gives a simple illustration of these facts. Diagrams on an exaggerated scale show the path of rays towards the reproduction camera lens. The points A, B and C of the film correspond to A_1, B_1 and C_1 of the mask. In fig. 1 a, where the film and mask are identical in size, a contour disagreement between the rays reaching the lens will occur. A and A_1 thus each correspond to one ray directed towards the lens. The same thing applies to C and C_1, while B and B_1, which are situated on the extension of the longitudinal axis of the lens correspond to the same ray of light. By making the mask on a suitable enlarged scale, as shown in fig. 1 b, the contour difference will be wholly eliminated. Each of the points A_2, B_2 and C_2 has a ray in common with the corresponding points of the mask. The simplest way to produce this enlarged mask is to invert the path of the rays and to replace the lens by a source of light containing a luminous body of fairly small size. This principle is demonstrated in fig. 1 c. The author has used different types

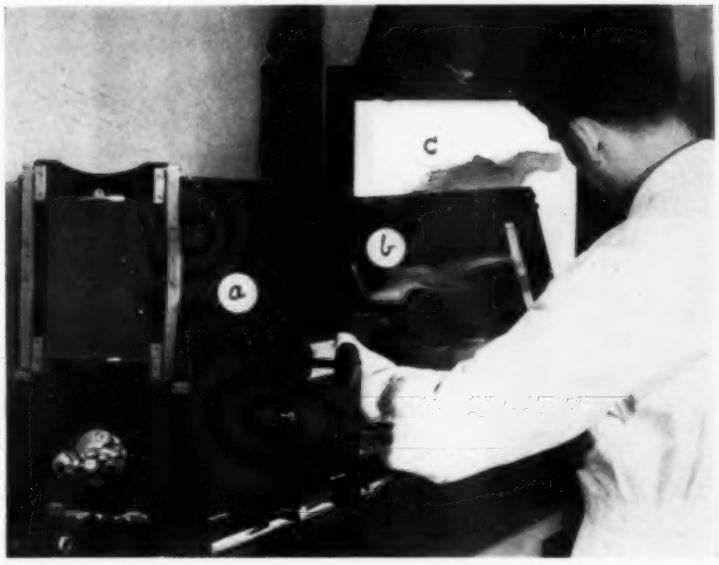

Fig. 2. Projection printing with contrast levelling using an ordinary reproduction camera (a). The mask (c) is in position, and the radiograph (b) between two framed glass sheets is being placed in front.

of lamps: a small opal bulb, about 40 mm in diameter, proved to be the most suitable at distances of ½ to 1 m. The source of light projects the radiograph on the paper which is to be used as a mask: both film and paper should be in the exact positions which they will occupy during the subsequent projection printing. A slight unsharpness in the mask is of no importance, especially in view of the subsequent diffusion. To prevent longitudinal stretching during processing, the paper should be wet when the exposure is made. The author has previously shown that wetting makes the paper stretch quickly to a size which is maintained during the whole of the processing. The wet paper is spread out by rolling on the opal glass plate which is to provide the illumination. Register marks for positioning are inscribed and the radiograph is placed in position between two glass sheets at a distance of about 1.5 cm from the mask. The exposure is made with the source of light which has replaced the lens. In order to obtain adequate faithfulness of detail, the source of light, as previously indicated, should be small. The exposure is followed by development which, for papers of the document type, is short (usually about 45 seconds). After rapid rinsing and about one minute of fixation followed

Fig. 3. The diffusion plate is inserted between mask and film.

by a few seconds of further rinsing, the wet mask is ready to be laid back on the opal glass plate and positioned by means of the registration marks. If desired, its position may be checked with the eye placed in the position of the camera lens. The mask is now ready, but if the reproduction be made at this point, the result will not be satisfactory. The paper structure of the mask will be obtrusive and the rendering of detail contours imperfect. The effect will be similar to that which is produced by laying a positive on a negative: certain details will all but disappear. The aim must be to introduce diffusion which will not affect the detail of the radiograph but spread the illumination of the various parts, caused by the mask, uniformly and evenly.

In the original contrast levelling method of contact printing, diffusion, as previously indicated, was produced by separating the mask and film by about 1 cm, the light thus reaching the film from all directions. In the present instance only those rays of light directed towards the lens are utilized and another method is necessary.

The easiest way of producing diffusion appeared to be by means of a sheet of fine ground glass of the type used in ordinary photography for focussing. The faint grain of the glass proved to be unimportant. The author employed a sheet of sand-blasted transparent plastic material

(Lucite, Plexiglas, Perspex) which proved to be suitable for the purpose. It should be placed between the mask and film, preferably as close to the latter as possible. It is a mistake to imagine that the diffusion will eliminate the need of magnification of the mask. In spite of the diffusion the actual rays of light are always mainly directed against the lens even if they pass through the diffusing sheet. With the mask, diffusion sheet and film in position, the exposure is made. As for direct contrast levelling work, "harder" paper may be used than for regular printing. Processing presents no particular problems.

Fig. 2 shows one phase of the projection printing procedure with contrast levelling, in which an ordinary reproduction camera (a) is employed. The mask (c) is in position and the radiograph (b) between two glass sheets in a frame, is being placed in front. The frame has guide pins which fit into corresponding sockets on the reproduction apparatus, so that it is always held in the same position and parallel with the opal glass sheet. Fig. 3 demonstrates how the ground glass is inserted between the mask and film. Fig. 4 is a reduced-scale contrast levelled print made as described (size of the original film: 30 by 40 cm — reduced to about 5 by 10 cm) and fig. 5 a negative print from a small positive on a lantern plate 8.25 × 8.25 cm from the same radiograph. The lantern plate provided an excellent positive for projection. Fig. 6, of an intravenous pyelogram, is a negative print, also made through the medium of a lantern plate. It appears that these latter are well suited as intermediaries for the making of negative contrast levelled reproductions either as paper prints or transparencies. In other cases, plates and films of the types used for copying continuous tone subjects and for general commercial work, *e. g.* 9 by 12 cm or 6.5 by 9 cm in size, seem to be most suitable. The final negative print of any size desired may be made in an ordinary photographic enlarger.

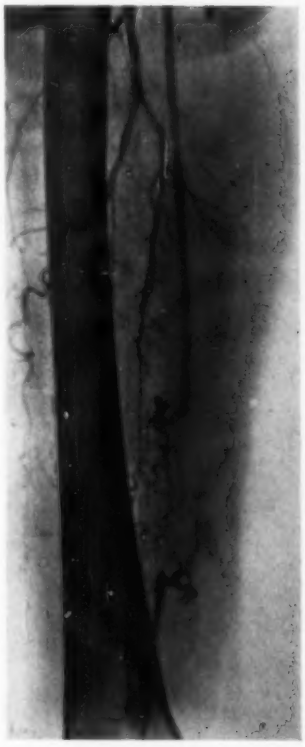

Fig. 4. Arteriography. Reduced-scale (approx. 1 : 4) contrast levelled print.

Naturally a fixed reproduction camera unit is not essential for the

Fig. 5.

Fig. 6.

Fig. 5. Negative made via a contrast levelled positive on a lantern plate from the same radiograph as Fig. 4.

Fig. 6. Urography. Reproduction via a lantern plate. Note richness of detail; small quantities of urine exuding from the ureteric orifices are visible.

production of reduced-scale contrast levelled prints. The principle is easily adapted to any camera and to any type of vertical or horizontal lighting, *e. g.* of the type used for viewing radiographs. Miniature cameras are suitable for making negatives via film positives. The cost of film is kept low: the making of lantern slides 24 by 36 mm for example is possible. A suitable supplementary front lens must naturally be employed in order to obtain a better scale of reproduction. Fig. 7 shows a print made from

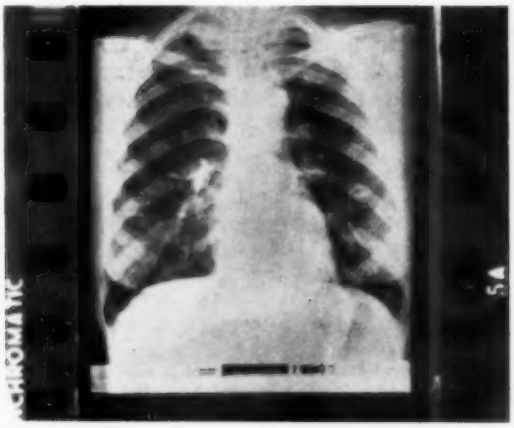

Fig. 7. Chest radiograph. Print made from a contrast levelled 24 × 36 mm positive on cine film.

a contrast levelled 24 by 36 mm positive on cine film (Camera: Leica/Elmar 1 : 3.5; aperture f: 9 for maximum definition). When using improvised lighting it is essential to shield the lens against stray light. If the illuminated area be larger than the film, it must be covered or masked off. The lens of the camera here reacts similarly to the eye and interfering sources of light will destroy the definition of dense areas (MATTSSON, 1952). Coated lenses are of considerable assistance in this respect.

Mention should be made of the production of contrast levelled negative prints from small size radiographs of 9 × 12 cm or less, *e. g.* dental films. The positive of the intermediary stage may be obtained by contact printing on a film or plate of the above-mentioned commercial type. The mask may be of single weight or thin document paper. Different results will be obtained depending on the contrast grades used. The distance between the masking print and radiograph necessary for diffusion is relatively small for the lesser film sizes. It may be determined by test in each individual case. To prevent the time of exposure for the fairly sensitive film or slide emulsions from becoming too short and hence difficult to control, a variable resistance controlling the voltage and thereby the intensity of the source of light behind the opal sheet may be introduced. The resistance may be set to calibrated values. Masking of the illuminated area around small films is essential, or stray light will cause interference. It should be mentioned that if the final print be made with an enlarger, it is possible to give prominence to certain parts by "dodging", etc., as in ordinary enlarging work.

In conclusion it may be said that reduced size contrast levelled prints are easy to make. Apart from a suitable camera, equipment ordinarily found in a radiographic department or photographic laboratory, or procurable at comparatively modest cost, is all that is required.

SUMMARY

The production of reduced positive and negative prints and lantern slides by contrast levelling is described. The method is a modification of the one for the contact printing of radiographs previously described by the author. A method of negative printing of small radiographs in their original sizes is also presented.

ZUSAMMENFASSUNG

Die Herstellung verkleinerter positiver und negativer Kopien und Diapositive mit Kontrastausgleich wird beschrieben. Die Methode ist eine Modifikation der vom Verf. früher beschriebenen Methode für Kontaktkopiieren von Röntgenbildern. Eine Technik zur Herstellung negativer Kopien kleiner Röntgenbilder in Originalgrösse wird ebenfalls beschrieben.

RÉSUMÉ

Description de la technique pour obtenir des épreuves positives et négatives et des clichés de projection par diminution des contrastes. Cette méthode est une modification de celle de reproduction des radiographies par contact, déjà décrite par l'auteur. Il décrit aussi une méthode de reproduction négative de petites radiographies dans leur format original.

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FROM THE 1ST ROENTGEN DEPARTMENT (DIRECTOR: DOCENT GUNNAR JÖNSSON),
SÖDERSJUKHUSET, STOCKHOLM, SWEDEN

THE APPEARANCE OF THE INTERNAL MAMMARY ARTERIES IN COARCTATION OF THE AORTA

by

Per Ödman

The abundant collateral system occurring in coarctation of the aorta may be observed to some extent both directly and indirectly even on conventional radiologic examination of the thorax. Thus, as a rule, it is possible to see the dilated left subclavian artery directly in the radiograph. Sometimes, the numerous collaterals in the superior aperture of the thorax may be observed in the radiograph, the superior mediastinum being wider than usual with its borders bulging toward the lungs. Indirectly, the existence of the collateral circulation may be inferred through the erosions caused by dilated tortuous intercostal arteries. According to MACLAUGLIN, erosions, produced by the tortuous and enlarged scapular circumflex artery, may also occur in the neck of the scapula.

The internal mammary arteries are among the most important vessels in the collateral system. These arteries will have been transformed into coarse, tortuous vessel stems close to the anterior thoracic wall, anastomosing, among others, with the intercostal arteries and continuing downward as the superior epigastric arteries. The internal mammary arteries are clearly shown in angiocardiography and thoracic aortography. However, in the majority of cases of aortic coarctation, it is possible also to visualize the dilated internal mammary arteries in a conventional radiograph of the thorax, obtained in a true lateral projection. They are seen close to the anterior thoracic wall as an entirely or partially continuous soft tissue band of varying width. This is in contrast to the adjacent lung parenchyma with its sharp, wavy border (fig. 1). Sometimes, double contours are seen here and there, due to the two vessels each forming contours against the lung (fig. 2). Posterior

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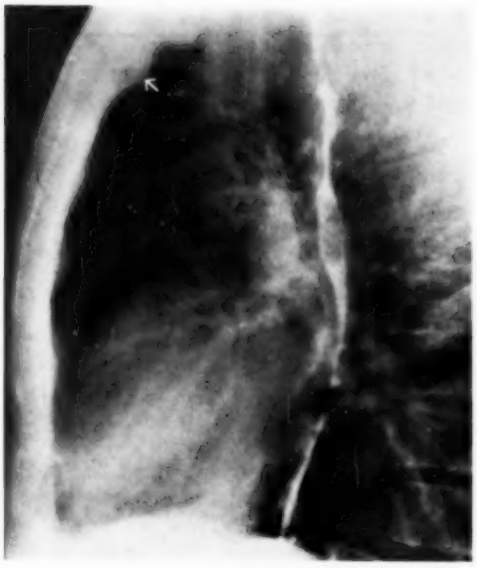

Fig. 1. Male, aged 32. Coarctation of the aorta. Thorax — lateral: A band of varying width may be seen close to the anterior thoracic wall of the lung contrasting to the sharp wavy border. It represents dilated internal mammary arteries. The clearly marked, denser portion posterior to the middle part of the manubrium (→), corresponds to tortuosities in the arteries.

to the manubrium sterni, the band narrows in a characteristic manner as it passes downwards. In this region it is sometimes possible to observe pulsations during fluoroscopy and to record them objectively by means of electrokymography (fig. 3). A small denser area is frequently found in this region and is characteristic of dilated internal mammary arteries.

The width and visibility of the internal mammary arteries in the radiograph are generally dependent upon their caliber, but the course and topography of the vessels also play a certain rôle. The arteries are frequently extremely tortuous, especially in the frontal plane. In lateral radiographs, these tortuosities are reproduced in different degrees of orthoprojection and is the explanation of the typical variations in density of the internal mammary arteries sometimes noticed. This is most apparent high up, posterior to the middle part of the manubrium sterni. As already mentioned, it is frequently possible to distinguish a clearly delimited, denser area, corresponding to marked tortuosities of the arteries at this level (figs. 4 and 5). Likewise the site of the arteries in relation to the sternum and the anterior extremities of the ribs has a certain significance. The corpus sterni and the retrosternal soft parts are projected more or less over the internal mammary arteries. The more the sternum is depressed into the thorax, the greater this superimposition will be and even greatly dilated, tortuous arteries may be entirely hidden by the sternum.

Fig. 2.

Fig. 3 a.

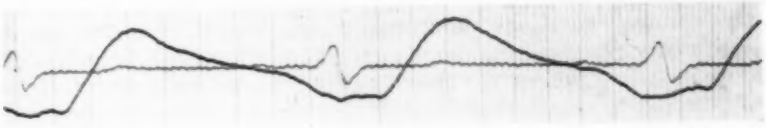

Fig. 3 b.

Fig. 2. Male, aged 8. Coarctation of the aorta. Thorax — lateral: The dilated interna mammary arteries are seen posterior to the sternum. In some places, double contours are evident.

Fig. 3. Male, aged 42. Coarctation of the aorta. a. The dilated mammary arteries lie posterior to the manubrium sterni. Pulsations observed during fluoroscopy. b. Typical arterial pulsations recorded in this area by electrokymography.

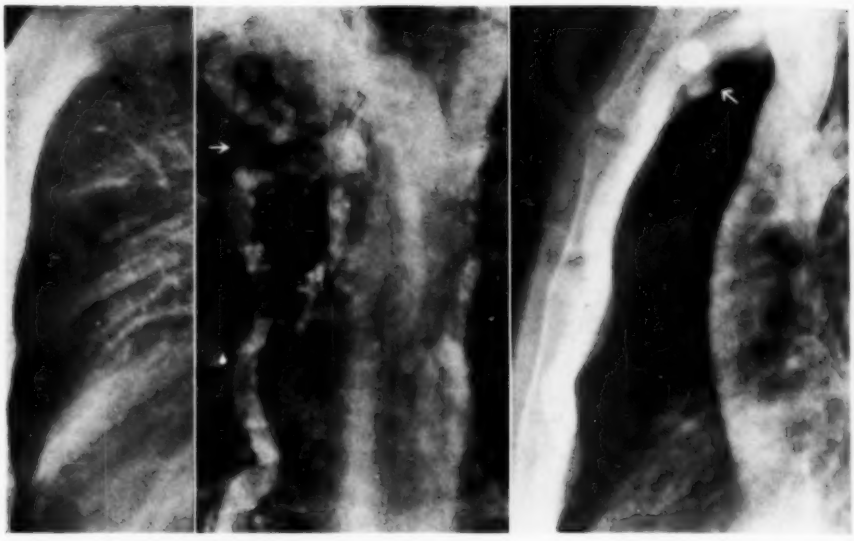

Fig. 4 a. 4 b. 4 c.

Fig. 4. Male, aged 28. Coarctation of the aorta. a. Conventional chest radiograph: The dilated internal mammary arteries are seen posterior to the corpus and manubrium sterni; at the level of the middle part of the manubrium, a rounded denser area (→). b. Thoracic aortography, anterior view: The internal mammary arteries filled with contrast medium and very tortuous at this level (→). c. Thoracic aortography, lateral projection: The orthoprojection of the contrast-filled internal mammary arteries corresponds in position to the denser area posterior to the middle part of the manubrium in *a* (→).

The importance of correct exposure technique must be pointed out in this connection. If the sternum is not depressed, it is possible in the majority of cases of coarctation of the aorta to show the internal mammary arteries in radiographs of the thorax taken by the usual method. However, it is possible to demonstrate the dilated arteries more clearly by means of a modified technique, the principle of which has been described by LAURELL. In our experience, the most suitable procedure is to obtain the lateral radiographs during deep inspiration, with a long focus—film distance (2.25 meters), a long object—film distance (30—40 centimeters) and using a high tube voltage (110 kV). The exposure time is 0.08—0.10 sec. A small primary aperture is used, so that a minimum area is exposed. A diaphragm is unnecessary, since by using a long object—film distance and a small primary aperture only slight secondary radiation will reach the film. A long object—film distance increases the blur

Fig. 5. Fig. 6.

Fig. 5. Female, aged 20. Coarctation of the aorta. Only suggestion of erosions of the ribs. Parts of the dilated internal mammary arteries markedly tortuous may be seen close to the anterior thoracic wall, at the level of the middle part of the manubrium (→). No other signs of the arteries.

Fig. 6. Aortic coarctation. The lateral radiograph has been obtained by the method described in the text: Focus—film distance 2.25 m, object—film dist. 30 cm and high voltage (110 kV). The internal mammary arteries are clearly shown (→).

of the image, but this disadvantage will be offset to a corresponding extent by the long focus—film distance. A high tube voltage makes it possible to use short exposure times and produces images of more harmonious contrast, which we have found to be an advantage (fig. 6).

The study of the internal mammary arteries directly in routine radiographs, affords opportunities of observing the condition of the collateral circulation in cases of aortic coarctation. Valuable information

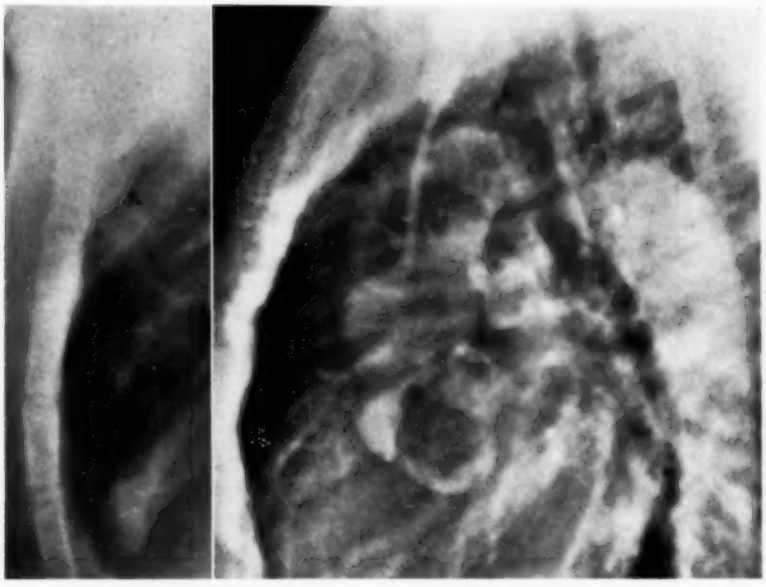

Fig. 7 a. 7 b.

Fig. 7. Male, aged 9. a. Conventional chest radiograph: The distal part of the aortic arch appears notably widened. The central vessels of the lungs unusually large. No erosions of the ribs. The internal mammary arteries may be seen close to the anterior thoracic wall at the level of the manubrium (→). b. Thoracic aortography: Stenosis in the aortic arch with atypical situation proximal to the origin of the left subclavian artery. In addition, there is a patent ductus arteriosus with a diameter of approximately 0.5 cm. It is evident that the post-manubrial changes (→) are caused by the dilated internal mammary arteries.

concerning these vessels may be obtained without the necessity of performing any examination demanding the injection of contrast media (thoracic aortography, angiocardiography). If dilated internal mammary arteries are observed, it is an indication of the presence of a collateral system. Such an observation may constitute an important diagnostic sign in atypical cases of coarctation of the aorta, in which the radiologic examination does not provide any other definite information of diagnostic value. It occurs in cases of aortic coarctation, for example, that the anatomic conditions are such that the superior mediastinum does not show characteristic changes in the radiograph (fig. 7). Likewise, erosions of the ribs may be absent. The latter occurs especially in cases of coarcta-

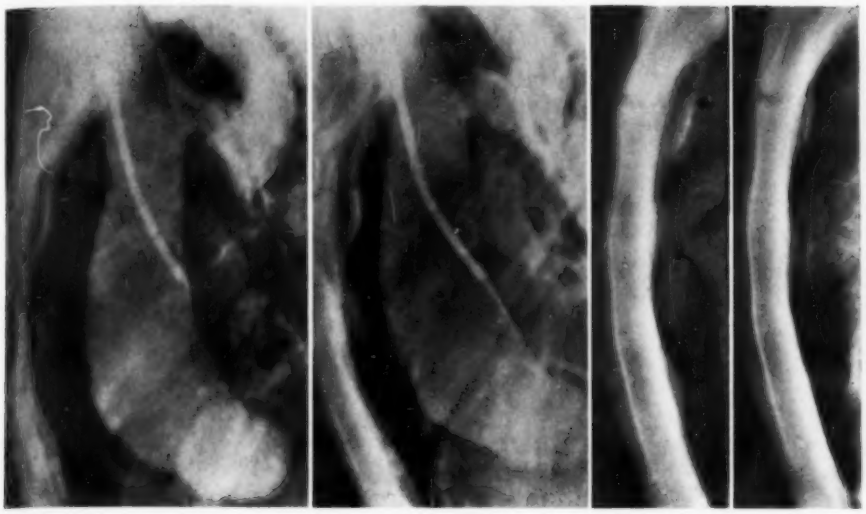

Fig. 8 a. 8 b. 8 c. 8 d.

Fig. 8. Male, aged 24. Coarctation of the aorta. a. Thoracic aortography: Total stenosis of the aorta a few centimeters inferior to the origin of the left subclavian artery; the internal mammary arteries greatly dilated and tortuous. b. Thoracic aortography 5 weeks after operation (resection of the aorta and end-to-end suture): Inconsiderable narrowing of the anastomosis; the internal mammary arteries have decreased in size. c. Routine radiograph before operation: The dilated internal mammary arteries may be seen posterior to the sternum (→). d. The internal mammary arteries have disappeared 7 months after operation.

tion in children in which the rib erosions have not had time to develop, and in aortic coarctation combined with patent ductus arteriosus.

The study of the dilated internal mammary arteries in the radiograph is of importance not only in the diagnosis of aortic coarctation but also in assessing the collateral circulation.

Thoracic aortography is carried out after the operation of coarctation, especially in order to diagnose possible postoperative aneurysms. The examination is therefore performed relatively soon after the operation (1 to 2 months). From such examinations, we know that the internal mammary arteries and other collaterals frequently decrease in size after the stenosis has been removed. The time interval between the operation and postoperative thoracic aortography is most often too short to permit any definite conclusions concerning the effect of the former upon the collaterals. These may be obtained, however, in a less elaborate manner

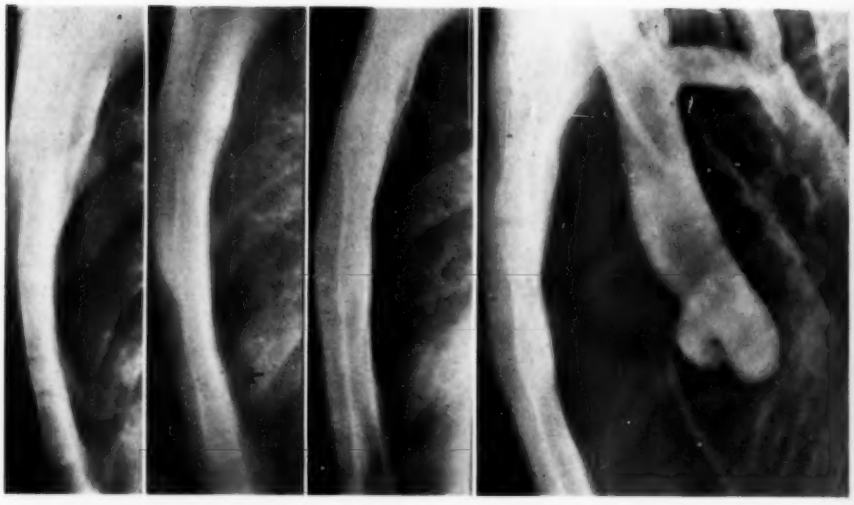

Fig. 9 a. 9 b. 9 c. 9 d.

Fig. 9. Male, aged 15 at the time of operation. Coarctation of the aorta. a. The dilated internal mammary arteries clearly observed in conventional radiograph before operation. b. 7 months, approx., after operation: The internal mammary arteries have decreased in size but are still visible (→). c. $4^1/_2$ years after operation: The internal mammary arteries have disappeared. d. Thoracic aortography, $4^1/_2$ years after operation: Only slight residues of the collateral system observed. The aortic arch is hypoplastic, but corresponding to the anastomosis, practically no stenosis remains.

by a study of the internal mammary arteries over a longer period in routine postoperative chest radiographs. It may be observed from such an investigation that in the most favorable cases the internal mammary arteries decrease in size relatively rapidly and disappear from the radiographs within a year (fig. 8). In other cases, this regression takes place more slowly and several years may elapse before the complete disappearance of the arteries occurs (fig. 9). Finally, it may sometimes happen that the internal mammary arteries remain unchanged (fig. 10). The regression appears to occur more slowly in relatively older patients, but the postoperative behavior of the collateral circulation depends mainly upon the anatomic conditions in and close to the anastomosis. There is frequently some residual stenosis at the site of the anastomosis. In addition, the arch and descending part of the aorta in numerous cases are hypoplastic with a relatively narrow lumen. The narrower these portions of the aorta, the more slowly regression of the dilatation of the internal mammary arteries takes place. When the aorta is so narrow that the

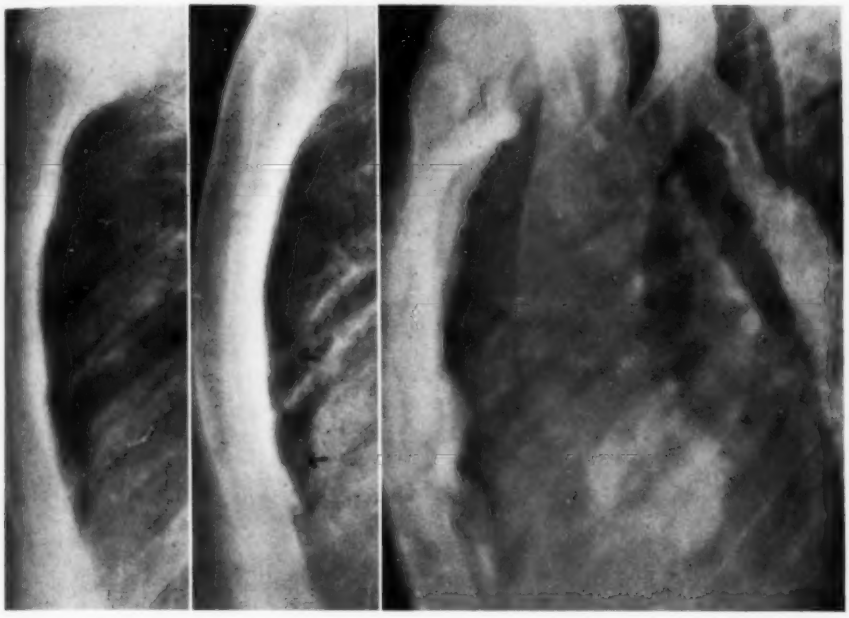

Fig. 10 a. 10 b. 10 c.

Fig. 10. Female, aged 22 at the time of operation. a. The dilated internal mammary arteries clearly visible in the preoperative radiograph. b. The internal mammary arteries remain considerably dilated $3^1/_2$ years after operation (→). c. Thoracic aortography, $3^1/_2$ years after operation: The aortic arch and the superior part of the descending aorta are hypoplastic. Narrow anastomosis, about the width of a pencil. Functioning collaterals are contrast-filled; among them, greatly dilated, tortuous internal mammary arteries.

collateral circulation is still necessary for a sufficient blood supply to the lower half of the body, regression is entirely precluded (cf. fig. 10). Accordingly, it is possible, to a certain extent, to determine the prognosis, or at least the effect of the operation on the collateral system, by postoperative radiologic observation of the internal mammary arteries.

SUMMARY

In cases of aortic coarctation, the dilated internal mammary arteries may frequently be observed in routine true lateral radiographs of the thorax. Knowledge of this possibility may be of importance in the diagnosis particularly in certain atypical cases. By postoperative radiologic examinations of the internal mammary arteries it is also possible to follow the condition of the collaterals after operative removal of the stenosis.

ZUSAMMENFASSUNG

In Fällen von Coarctatio aortae können die erweiterten Arteriae mam. int. häufig auf den üblichen seitlichen Röntgenaufnahmen des Thorax beobachtet werden. Diese Tatsache kann besonders für die Diagnose gewisser atypischer Fälle dieser Missbildung von Bedeutung sein. Das Studium der Art. mam. int. bei postoperativen Röntgenuntersuchungen gibt auch die Möglichkeit, das Verhalten der Kollateralen nach operativer Entfernung der Stenose bei der Coarctatio aortae zu studieren.

RÉSUMÉ

Il est fréquent, dans des cas de coarctation aortique, que l'on puisse voir, sur des radiographies de profil strict du thorax, l'artère mammaire interne dilatée. Il peut être important pour le diagnostic de connaître cette possibilité, en particulier dans certains cas atypiques. Des examens radiographiques post-opératoires des artères mammaires internes permettent aussi de suivre l'évolution des collatérales après la résection chirurgicale de la sténose.

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FROM DEPT. OF PHYSICS, LABORATORY ANTONI VAN LEEUWENHOEK-HUIS OF THE NETHERLANDS CANCER INSTITUTE, AMSTERDAM, THE NETHERLANDS

EXPERIMENTS WITH INTERCAVERNOUS ROENTGEN IRRADIATION AND SO-CALLED COLLIMATOR GRIDS

by

M. Sangster

A number of experiments have been carried out in our Institute in order to determine better dosage of parametrial irradiation in more advanced cases of carcinoma portio uteri.

Only a small percentage of the energy produced by various conventional methods of additional roentgen irradiation actually reaches the site of the tumour; it is, moreover, very difficult to spare the extremely radiosensitive rectal papillae. Attempts were made to avoid these disadvantages by intercavernous irradiation via the vagina.

One of the possibilities under investigation is based on the following considerations:

1. The bundle of rays emitted by a normal 200 kV therapy tube is passed through a leaden tube placed in the vagina. One side of this tube is open and the end is closed. It contains scattering material. Since the dose inside this tube can be arbitrarily large, a large quantity of scattered radiation will reach the parametrium via the vaginal wall.

2. In order to increase the percentual depth dose of this scattered radiation, a so-called collimator grid is used. A collimator grid consists of a number of tubular ducts with walls of absorbing material and arranged in a parallel or convergent fashion. If this grid be placed immediately in front of a source of radiation, the absorbing effect on points near the grid is more marked than that on more distant points. In this manner, compensation is obtained for the inconvenient steep decrease in the dosage with distance, in the vicinity of a source of radiation. The grid constitutes a means of filtering from a divergent bundle emitted by a radiating plane a portion with parallel or convergent properties.

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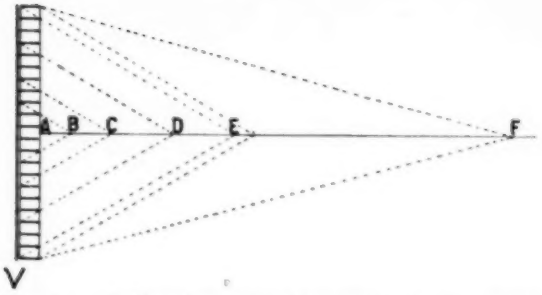

Fig. 1. a. Collimator grid with a radiation source V placed behind.

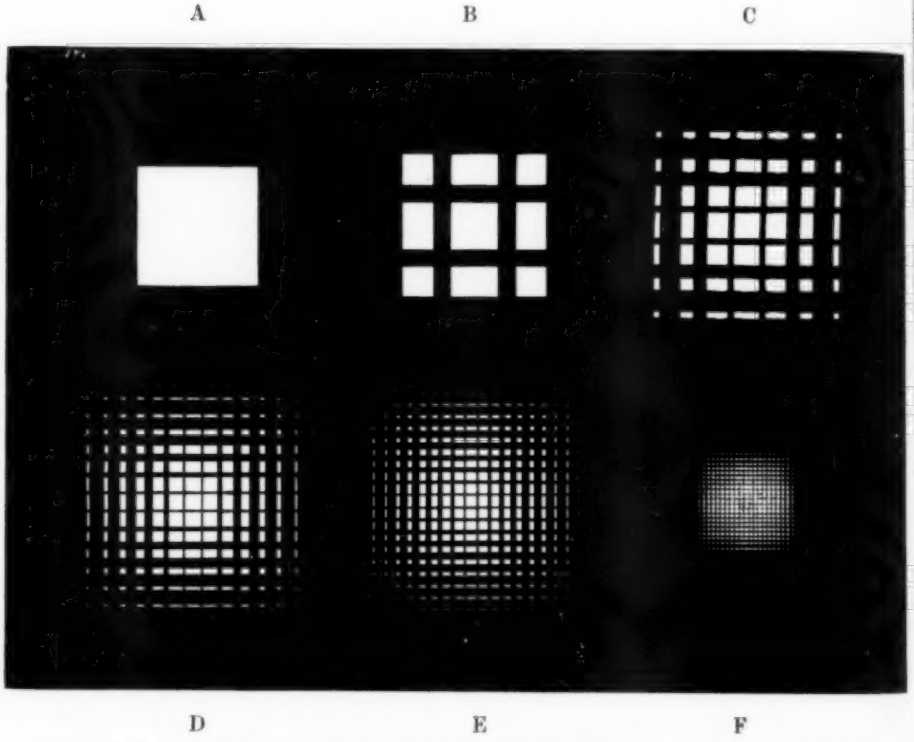

Fig. 1 b. V as seen through the collimator grid, from the points A to F, respectively. The total area of the white squares will be proportional to the spatial angle under which one sees the surface V through the filter, thus with the intensity in the concerning point.

This may be elucidated with the aid of a more or less equivalent optic model. The grid with its tubular ducts should be presumed to be placed in front of a plane-shaped light source V (Fig. 1 a and b). In the first instance, absorption and scattering are neglected.

It is obvious that the intensity at a certain point is directly proportional to the spatial angle under which the plane V is viewed from this point (*i. e.* the size of the apparent surface of V, divided by the square of the distance).

Fig. 1 b shows what is observed when the eye is situated at points A—F, successively. Although the size of the white squares decreases with an increase in distance, we see that compensation is obtained inasmuch as the number of tubes passing light gradually increases.

As a result, the intensity at the points A—E is practically constant; it gradually decreases at greater distances, when all tubes begin to pass light. The screening effect of the grid therefore approaches 0 when the distance is further increased.

A number of calculations were made on parallel collimator grids. The dose distribution obtained, neglecting scattering and absorption, is given in Fig. 2 a and b. The dose distribution obtained without the grid is shown for comparison.

It was found that the dose was about 100 % throughout an approximately pyramidal region. The properties of the filtered bundle are therefore entirely those of a parallel one. The intensity in the immediate vicinity of the grid may show slight fluctuations; however, these may be presumed to offer few difficulties in practice. Outside this region, gradual divergence is observed. Since the units of the x and y co-ordinates on which these curves are based are dimensionless, they may be adjusted in any particular case.

The grid constant, *i. e.* the length : width ratio of the tubular ducts, is determined by the ratio of the units to which the values found are reduced.

It is self-evident that the absolute dose value corresponding to the 100 % value is much less when a collimator grid is used. In this case, the ratio is 1 : 100.

A definite disadvantage lies in the fact that the width of the half shadow region of the bundle becomes greater with an increase in the distance to the grid. When some divergence is permissible, however, a reasonably wide region can be irradiated within the dose curve of 50 %. It is obvious, however, that a convergent arrangement of the tubular ducts of the grid is generally of little use, as the region irradiated would then be very restricted. Collimator grids were introduced by RAHM (3) and later used by MARAGHAMO (2).

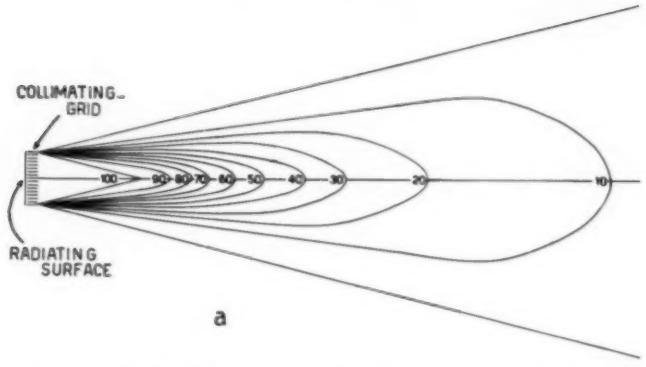

Fig. 2 a. Dosis-distribution as calculated for a square radiation source. Scattering and absorption are omitted.

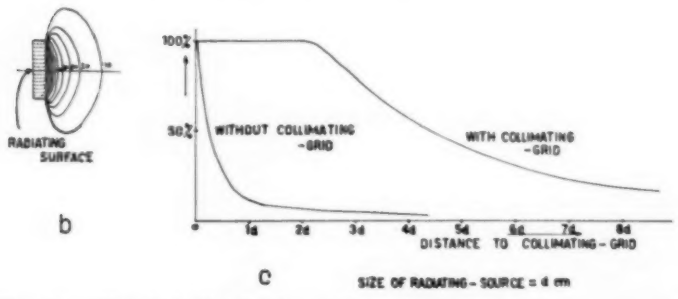

Fig. 2 b. The dosis-distribution without collimator grid as compared with fig. 2 a.

c. The procentual depthdosis at the axis calculated with and without collimator grid.

In my opinion, it is still insufficiently realized that these grids are especially useful in intercavernous irradiation, offering as they do the possibility of obtaining a reliable homogeneous dose-distribution in the direct vicinity of a source of radiation.

In our experimental attempts to improve parametrial irradiation, we made use of the above-mentioned scattered radiation applicator furnished with a collimator grid. The results of dose determinations in a water phantom on this applicator are given in Fig. 3.

The possibility of increasing the penetrative power of a SIEMENS-CHAOUL tube with the aid of a collimator grid will be investigated in the near future.

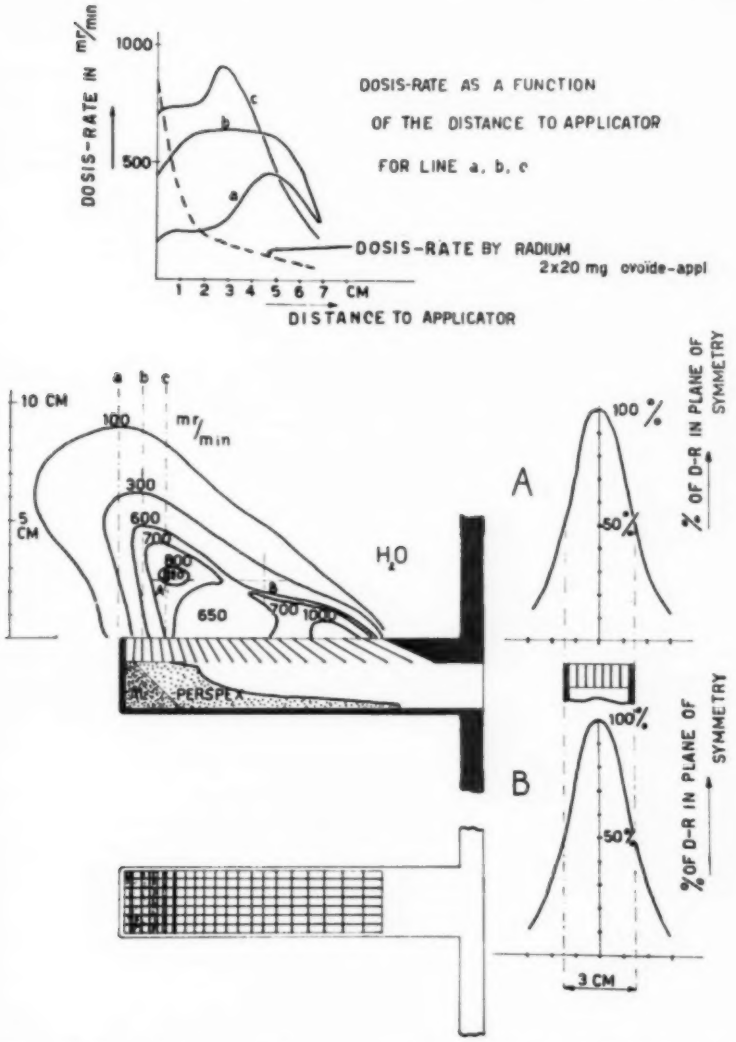

Fig. 3. Determinations made on a scattered radiation applicator with collimator grid. The applicator is surrounded by water, the interior being partially filled with scattering material, while the remaining spaces are filled with air. The focus of a 200 kV 25 ma tube (biphasic rectification, with 0.5 mm Cu and 1.25 mm Al filters) is situated centrally at a distance of 10 cm from the entrance of the applicator.

Finally, I should like to mention investigations into the use of radioactive applicators.

The restrictions in the use of radium and cobalt are primarily attributable to the fact that the hardness of the irradiation practically precludes partial screening inside the body.

One of the possibilities under investigation is the use of an aimed Ir^{192} applicator.

We expect to obtain a useful applicator by placing an Ir^{192} source of 2 mm diameter and 2 mm length in the centre of a uranium bullet with a diameter of 25 mm, a sector of the bullet being removed, thus obtaining what might be described as a miniature roentgen tube or bomb, which can be brought inside the body.

Attempts will be made to determine the extent to which this applicator makes it possible to cross-irradiate the parametrial region by intercavernous vaginal irradiation.

The possibility of a collimating grid combined with a plane-shaped isotope γ-radiation source (50—100 kV) will be investigated. In this manner, we may obtain a radiation applicator measuring say 50 mm Ø and 6 mm thick and emitting a bundle with, in a certain region, characteristics of a parallel bundle. In principle, this applicator would furnish a most satisfactory means of intercavernous irradiation of the portio uteri and the parametria. For instance, two fields could be aimed at the parametria from the vagina, while irradiation would be completed by the insertion of radium into the cervix. The present isotope of choice for this method is Tm^{170}; it has been obtained in a fairly concentrated condition by Mr. ROBERT WEST of Harwell.

Further data on these experiments will be published later.

I should like to thank my colleague, Dr. C. G.'t Hooft for his assistance in the phantom measurements, Mr. H. Lokkerbol, our radiologist, for his advice on medical matters and Mr. M. J. Bergström and Mr. J. J. L. Koenen (instrument makers) for their zeal and care in the construction of the lead applicator.

SUMMARY

The paper deals with a number of new possibilities of improving dose distribution in the parametrium in more advanced cases of carcinoma portio uteri by intercavernous irradiation via the vagina. A new type of applicator is described, based on utilization of the scattered radiation of a primary bundle of roentgen rays and on the use of a collimator grid. The results of phantom determinations made on this applicator are given. The action of a collimator grid is elucidated by an optic model and the insight gained is further increased by means of calculations. Mention is made of investigations now being made into the use of γ-ray applicators.

ZUSAMMENFASSUNG

Der Verf. zeigt neue Möglichkeiten dazu auf, in fortgeschrittenen Fällen von Cancer colli uteri mit intrakavitärer Bestrahlung durch die Vagina eine bessere Verteilung der Dosis im Parametrium zu erzielen. Ein neuer Applikator wird beschrieben, mit welchem die Streustrahlung eines primären Röntgenbündels und ein Kulissenfilter benutzt wird. Die Ergebnisse von Phantommessungen mit Hilfe dieses Applikators werden mitgeteilt. An Hand eines optischen Modells wird eine anschauliche Vorstellung über die Wirkung des Kulissenfilters gegeben. Eine Berechnung ermöglicht ein tieferes Verständnis.

Zum Schluss werden noch einige im Gange befindliche Versuche erwähnt, wobei γ-Strahler zur Erreichung des gestellten Zieles benutzt werden.

RÉSUMÉ

Cet article a pour but d'indiquer quelques nouvelles possibilités d'obtenir une meilleure répartition des doses dans le tissu cellulaire du ligament large de l'utérus au moyen d'une irradiation intracavitaire par voie vaginale dans des cas très avancés de cancer du col utérin. Un nouveau type d'applicateur est décrit. On se sert ici du rayonnement diffusé d'un faisceau de rayons roentgen primaire et d'un diaphragme de «collimation».

Les résultats de mesures sur fantôme faites avec cet applicateur sont donnés. L'action des diaphragmes de collimation est démontré à l'aide d'un modèle optique. Un calcul permet une compréhension plus profonde. Enfin mention est faite de quelques expériences en cours, où des sources de rayons γ sont employées pour atteindre le but indiqué.

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CONTRIBUTION DE LA RADIOCHIMIE A LA RADIOBIOLOGIE

par

C. Piffault, J. Duhamel et *D. Longuet*

En 1942, LACASSAGNE, utilisant comme matériel biologique d'expérience la souris nouveau-née en état d'asphyxie a montré une perte de sensibilité à l'action des rayons roentgen chez ces sujets, par privation d'oxygène. Ce fait est général et a été étudié par THODAY et READ sur la fève. Certains corps soufrés importants dans le métabolisme de l'oxygène jouissent de propriétés analogues et interviennent comme radioprotecteurs: c'est le thème des travaux de LATARGET et EPHRATI sur les bactériophages et l'acide thioglycolique, de MOLE sur les mammifères et la thiourée, de PATT, SMITH, TYREE et STRAUBE, HERVÉ et BACQ sur la souris et la cystéine.

Quel que soit le mécanisme exact de cette radioprotection, mécanisme encore relativement obscur, nous devons en retenir, d'un point de vue biologique, l'intervention de l'oxygène. Les expériences que deux d'entre nous ont faites avec P. BLANQUET ont permis de préciser qu'on pouvait obtenir par irradiation de la cystéine et de l'hyposulfite de soude, un procédé de dosage de l'eau oxygénée fournie par l'irradiation de l'eau aux rayons roentgen.

D'autres corps réducteurs, non soufrés, sont aussi des radioprotecteurs: c'est le cas du glucose étudié sur le lapin par LOISELEUR et BACLESSE. Le glucose est un polyalcool et un réducteur. On sait, depuis longtemps (LAZAREFF), qu'un trialcool, peu réducteur, la glycérine, jouit en photochimie de propriétés très particulières. Son étude, à ce point de vue, a été faite en détail par J. PERRIN, et lui a permis d'édifier une théorie des actions photochimiques dont les applications numériques sont parfois contestables (C. PIFFAULT, P. BLANQUET, J. DUHAMEL), mais qui, dans l'ensemble, demeure stable à l'heure actuelle.

Remis à la Rédaction le 15 juin 1952.

Lorsqu'on mélange certains colorants à la glycérine, et qu'on expose la solution à la lumière, on constate la formation d'un composé labile, en général incolore, qui se recolore à l'obscurité, spontanément, en présence d'air, même à l'état de traces, mais qui persiste indéfiniment dans le vide. Des expériences très simples montrent que c'est l'oxygène de l'air qui est actif. On a donc formation d'un leuco-dérivé régénérant le corps coloré en présence d'oxygène: c'est typiquement un phénomène d'oxydo-réduction, et il ne faut pas s'étonner que le corps étudié le plus en détail, en présence de glycérine, soit le bleu de méthylène.

Indépendamment de l'importance théorique de ce phénomène, l'intérêt biologique en est grand: en effet, la glycérine est très répandue dans l'organisme comme constituant des graisses et, d'autre part, nous fermons en quelque sorte le cycle, en nous ramenant à un phénomène d'oxydo-réduction à peu près pur. LEVAILLANT a étendu les travaux de PERRIN à d'autres corps organiques: polyalcools, acides-alcools, certains acides gras qui se comportent comme la glycérine, avec naturellement plus ou moins d'aisance. Tous ces corps sont très répandus dans l'organisme animal ou végétal, et l'intérêt biologique de ces expériences est à priori très important.

Ces études ont été faites à la lumière visible, au proche infra-rouge (jusqu'à 3 μ), et au proche ultra-violet. Nous avons tenu à les reprendre en utilisant l'infra-rouge jusqu'à 7 μ, et les rayons roentgen. Ceux-ci étaient fournis par un tube à anticathode de cuivre, alimenté en tension constante (24 KV) sous 20 mA de débit, avec filtre de 10 μ d'aluminium, et fournissant un rayonnement dont la longueur d'onde était de l'ordre de d'$^1/_2$ Å. La réaction, comme nous l'avons dit, réversible avec la glycérine, est irréversible dans l'eau, matériel habituel des radiochimistes, comme l'avait déjà signalé LEVAILLANT; nous avons systématiquement comparé le comportement des mêmes corps dans l'eau et dans la glycérine.

Les substances soumises aux rayons roentgen étaient irradiées en goutte pendante jusqu'à décoloration suivant la technique que nous avons décrite par ailleurs; le temps moyen d'irradiation était d'une dizaine de minutes. Pour l'exposition aux infra-rouges, nous nous sommes servis d'une étuve fonctionnant comme corps noir à 130° (et émettant des infra-rouges de 7 μ) pendant 5 heures, ou d'une lampe «Infraphil» pour le visible et le proche infra-rouge, avec interposition éventuelle d'un filtre (solution trouble saturée de sulfate de cuivre, sous 20 cm. d'épaisseur, pour éliminer l'infra-rouge et l'ultra-violet) pendant plusieurs dizaines d'heures. Avec ce système, nous pouvions traiter les substances en ampoules scellées de quelques centimètres cubes, ce qui offrait un petit avantage technique; en effet, lorsqu'il se forme un leuco-dérivé dans la solution glycérinique, il se recolore par l'exposition à l'air, à l'obscurité, à cause de la viscosité de la glycérine il ne diffuse pas, et il se forme à

partir de la surface de la solution, une zone colorée s'étendant sur quelques millimètres et tranchant sur le leuco-dérivé non oxydé.

Ce test est très net, en il permet de se rendre compte qu'une solution a pâli sans se décolorer sensiblement; en effet, s'il s'est formé un peu de leuco-dérivé, il y a recoloration en surface, formation de la zone qui tranche sur le reste de la solution à peine pâli. C'est ainsi qu'on peut étudier les corps peu sensibles.

Dans l'eau dégazée par contre, la recoloration des leuco-dérivés s'étend pratiquement à toute la masse.

Les solutions étudiées doivent être assez diluées (1/10,000 ou 1/5,000). Enfin, bien entendu, on doit vérifier la neutralité du verre des ampoules; pour cela, nous avons traité de la même façon des ampoules choisies au hasard, où nous avions placé des indicateurs de pH (phtaléine de phénol en solution aqueuse basique ou neutre, phénol-sulfone-phtaléine, bleu de bromothymol, pourpre de bromocrésol et rouge neutre) qui, dans nos conditions de travail, n'ont pas changé de couleur au cours de l'expérience, sauf le rouge neutre qui se comporte en colorant d'oxydo-réduction.

Nous avons préparé des séries de quatre ampoules de chaque corps: une ampoule témoin sous vide (bon vide primaire créé à l'aide d'une pompe à palette dans l'huile), une ampoule pour irradiation sous vide, une ampoule pour irradiation sous atmosphère inerte (CO_2), une ampoule pour irradiation en présence d'air.

Une fois les ampoules scellées à moitié pleines, puis irradiées, nous avons suivi leur comportement pendant trois semaines à l'obscurité; c'est là qu'on voit apparaître, au bout d'un temps variant de quelques heures à quelques jours la zone colorée en surface, dans les ampoules contenant de l'air. Au bout de ce temps, nous avons cassé les ampoules, sauf l'ampoule témoin, et contrôlé leur évolution.

Pour l'exposition aux rayons roentgen en goutte pendante, nous avons été obligés de travailler en présence d'air.

Nous avons étudié le bleu de méthylène, le bleu de toluidine, le bleu de thionine, le bleu azur, le bleu de Nil, le vert janus, tous colorants d'oxydo-réduction. Le rouge neutre se comporte comme les corps précédents, mais il y a confusion des teintes avec celles qu'il prend en tant qu'indicateur de pH et nous n'en tiendrons pas compte.

Pour la clarté de l'exposition, nous séparerons les corps étudiés en trois catégories:

1°) Le bleu de méthylène, le bleu de toluidine, le bleu de thionine, le bleu azur, ont, sous toutes les formes d'irradiation, que nous avons utilisées, le même comportement.

En solution glycérinée, ils changent de teinte donnant une solution incolore pour le bleu de méthylène et le bleu de toluidine et le bleu azur,

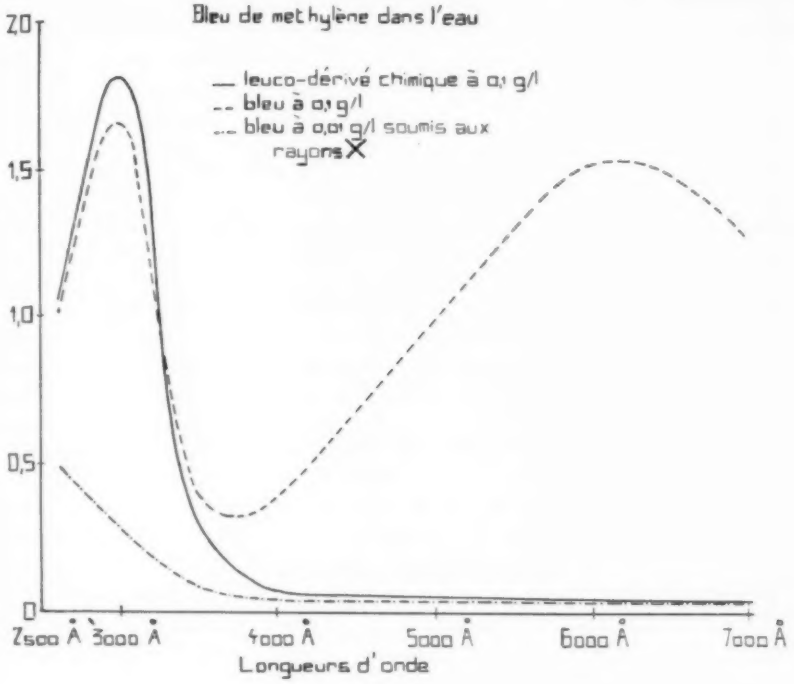

Fig. 1.

légèrement brune pour le bleu de thionine. Ces aspects sont toujours réversibles, et la solution reprend sa teinte primitive au contact de l'air après l'irradiation. Dans tous les cas, cette recoloration commence par la zone de contact de la solution avec l'air. Nous avons même pu constater que lorsque l'épaisseur du liquide est grande, la recoloration n'atteint pas le fond du récipient, même en attendant plusieurs mois.

En solution aqueuse, il faut distinguer le mode d'exposition.

Pour les rayons roentgen, on obtient la décoloration, mais le phénomène n'est pas réversible, et à quantités de liquide égales, nécessite une irradiation plus longue (variant du double au quadruple suivant le corps) que la décoloration dans la glycérine.

Pour l'infra-rouge, on n'arrive jamais à la décoloration.

Il semble que la zone de longueurs d'onde de transition est située dans le visible; en effet, les solutions aqueuses pâlissent spontanément à la lumière solaire au bout d'un temps assez long.

La glycérine semble donc étendre vers les grandes longueurs d'onde

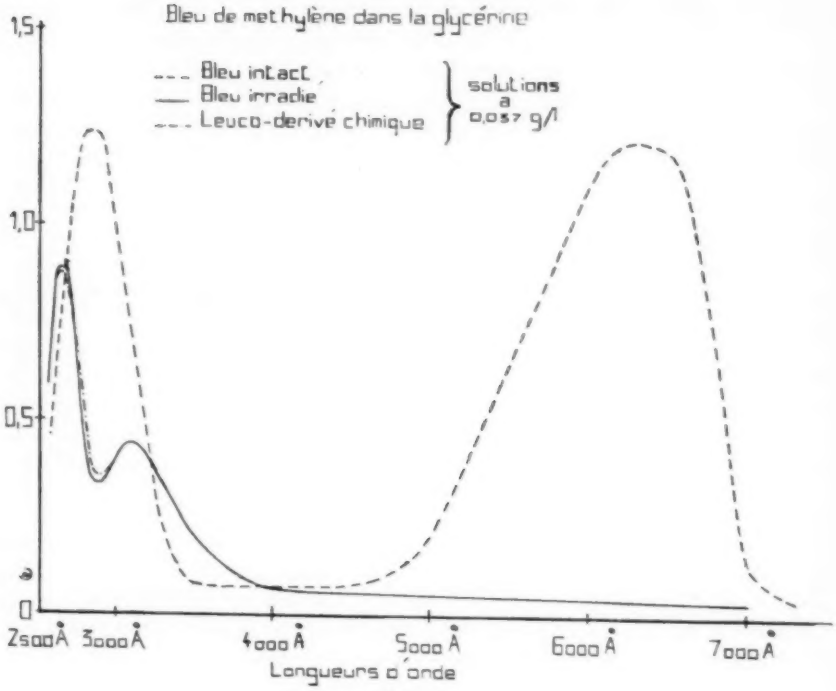

Fig. 2.

l'action décolorante des radiations électro-magnétiques. Elle jouit de propriétés sensibilisantes mais permet la réversibilité du phénomène.

2°) Le bleu de Nil est très particulier.

En solution glycérinée, il se décolore aux rayons roentgen, donnant un composé labile qui reprend sa teinte initiale; aux infra-rouges, par contre, il n'est pas altéré.

En solution aqueuse, il se décolore irréversiblement aux rayons roentgen comme à l'infra-rouge.

La glycérine jouit donc des mêmes propriétés que dans les groupes précédents, vis-à-vis de lui, mais dans le domaine des courtes longueurs d'onde seulement. Dans les infra-rouges, elle est protectrice.

3°) Le vert-janus:

En solution glycérinée, il donne une solution bleu-verdâtre virant au mauve sous l'action des rayons roentgen et des infra-rouges. Ce virage n'est pas réversible. (Le corps coloré violet ainsi obtenu possède un com-

portement particulier en présence de lumière visible et pour de très longues irradiations (plusieurs jours): il forme un leuco-dérivé réversible.)

En solution aqueuse, il y a décoloration brutale au bout d'un temps assez long aux rayons roentgen. A l'infra-rouge, sous vide, et sous CO_2, la solution vire au mauve de façon stable, mais la solution en présence d'air reste bleu sale.

Le comportement de ce corps est exceptionnel dans la longue liste des corps étudiés, et dont nous ne retenons que les colorants d'oxydo-réduction. Nous le citons pour mémoire, et pour souligner sa rareté eu égard au nombre de substances qui se comportent comme celles des groupes I et II et à celles qui ne réagissent pas à l'irradiation.

Lorsqu'on étudie les corps réversibles, on peut se demander quel est l'état dans lequel ils se trouvent après irradiation, et si on assiste réellement au cours de leur recoloration à une «restitutio ad integrum». Le plus facile à étudier est le bleu de méthylène qu'on peut vraiment considérer comme le type de la série. C'est ce qui explique qu'il ait servi aux études de LAZAREFF, de J. PERRIN, de LEVAILLANT et, plus récemment de SHEKTMAN et de ses collaborateurs. Nous l'avons étudié nous-mêmes depuis l'action des rayons γ jusqu'à celle des infra-rouges par la photométrie à l'aide du spectrophotomètre décrit par A. LALLEMAND, C. PIFFAULT et P. BLANQUET. Les figures montrent les résultats obtenus dans le cas de l'eau et dans celui de la glycérine. On y constate que le bleu de méthylène est caractérisé par deux bandes d'absorption, l'une vers 2,900 A, l'autre dans le vert et le rouge.

Après passage aux rayons roentgen, il ne reste rien des deux bandes, en solution aqueuse, si on compare avec le leuco-dérivé obtenu par voie chimique, on voit que celui-ci conserve la bande ultra-violette.

Au contraire, en solution glycérinée, le spectre obtenu est identique à celui du leuco-dérivé chimique, ce qui traduit l'identité de nature chimique des deux corps.

Le spectre, après recoloration, est identique à celui de la solution initiale: il y a bien reconstitution *complète*. Les résultats sont analogues pour les autres bleus, l'évolution semblable.

Ainsi, la glycérine manifeste son action sur ces indicateurs de rH en les sensibilisant aux radiations, c'est-à-dire, en accélérant leur vitesse de décoloration, mais ne permet, par contre, que la création de leur leuco-dérivé, et rend réversible la réaction au contact de l'air.

Cette sensibilisation se traduit également par une extension vers les grandes longueurs du domaine où le test photochimique de décoloration peut être mis en évidence.

Le mécanisme de ces transformations est encore obscur.

L'explication la plus poussée est celle de PERRIN qui conduit à une conclusion inadmissible; la radiation active est de 3.2 μ, ce qui est con-

trouvé. Il nous suffit de savoir, d'un point de vue biologique, qu'il est lié à des réductions (formation de leuco-dérivé), et à des oxydations (recoloration). LAZAREFF a démontré qu'en milieu aqueux, il s'agit d'oxydations irréversibles avec destruction de la molécule. Contrairement à ce que pensait J. PERRIN et LEVAILLANT, la présence ou l'absence d'air, une atmosphère inerte ne jouent aucun rôle dans le processus de décoloration, ce qui est, biologiquement, important.

Il faut remarquer, de plus, qu'il est très possible que les radiations actives en milieu aqueux et en milieu glycériné, n'appartiennent pas au même domaine: c'est ce que montre le bleu de Nil où l'infra-rouge est inactif sur la solution glycérinée.

Fait remarquable, la glycérine agit sur des colorants qui ne sont pas indicateurs d'oxydo-réduction, en permettant, par irradiation, la formation d'un dérivé qui reprend, au repos, la teinte primitive par exposition à l'air; c'est le cas de l'éosine étudiée aux infra-rouges par LEVAILLANT, et dont nous avons poussé l'étude aux rayons roentgen. C'est aussi celui de l'aniline verte.

Un autre point important est que ces réactions en milieu glycériné sont indéfiniment reproductibles.

Il n'est pas absurde de penser que les substances oxydo-réductrices existant dans les organismes vivants, puissent se comporter comme les indicateurs colorés que nous venons d'étudier, c'est-à-dire, de façon réversible; le cas des modifications irréversibles (vert janus) étant assez rare.

Si on songe à la complexité des liquides organiques, et en particulier à leur teneur en lipoïdes (avec acide gras et glycérine), on voit qu'il est peut-être imprudent d'extrapoler sans restrictions les expériences faites en milieu aqueux et les raisonnements qui s'y réfèrent.

Au niveau des êtres organisés: mono- ou pluricellulaires, le problème est encore plus complexe, certains facteurs intervenant dans le transport d'énergie, du rayonnement au corps récepteur, voyant leur action modifiée en fonction des proportions relatives des constituants de la membrane cellulaire, ainsi que l'ont montré l'un de nous et G. MEYNIEL sur des cellules libres.

Chez la souris, cette radioprotection semble liée, d'après LEBLOND et SEGAL, DOUGHERTY et WHITE, à une perturbation de la décharge lipoïdique surrénalienne, décharge liée à l'irradiation de l'organisme. Les substances qui possèdent le même effet sont radioprotectrices (G. BETZ et H. VAN CAUWENBERGHE). C. PIFFAULT avait déjà signalé en 1934 le rôle protecteur de certaines substances anti-stress et des lipoïdes. PATERSON et MATTHEWS ont récemment mis en évidence le pouvoir protecteur de l'alcool. La radioprotection par la glycérine entrerait donc parfaitement dans le cadre général délimité par les lipoïdes et les alcools, et le

comportement des colorants d'oxydo-réduction serait dans ce cas une contribution importante à la connaissance du mécanisme de la radiobiologie.

RÉSUMÉ

Certains lipoïdes possèdent un pouvoir radioprotecteur pour les monocellulaires. Des travaux récents font jouer un rôle dans la radioprotection des organismes élevés à une modification de la décharge lipoïdique surrénalienne. On étudie spectrométriquement dans le présent travail l'effet radioprotecteur d'un constituant des lipoïdes, la glycérine, sur plusieurs colorants d'oxydo-réduction, effet protecteur dont le mécanisme est lié à la présence d'oxygène dans le milieu, ce qui confirme quelques résultats récents.

SUMMARY

Certain lipids possess a protective effect against irradiation of unicellular organisms. Some recent studies indicate that a modification of the suprarenal emission of lipids plays a rôle in the protection against irradiation in higher organisms. In the present investigation, a spectrophotometric study is made of the protective effect of one constituent of the lipids, glycerol, upon several coloured oxydo-reduction tests. The mechanism of this effect is found to be associated with the presence of oxygen in the environment, a fact which confirms some recent results.

ZUSAMMENFASSUNG

Gewisse Lipoide besitzen die Eigenschaft, einzellige Lebewesen gegen jonisierende Strahlung schützen zu können. Neuere Arbeiten machen geltend, dass eine Veränderung der lipoiden Nebennierensekretion hierfür eine Rolle spielt. In der vorliegenden Arbeit wird die Strahlenschutzeigenschaft eines Glyzerinlipoides vom spektrometrischen Standpunkt aus analysiert. Der Schutzmechanismus hängt mit dem Sauerstoffvorkommen im Milieu zusammen; dieses bestätigt einige kürzlich gewonnene Ergebnisse.

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FROM THE FIBIGER LABORATORY OF THE UNIVERSITY INSTITUTE OF PATHOLOGIC ANATOMY (DIRECTOR: PROFESSOR J. ENGELBRETH-HOLM), COPENHAGEN, DENMARK

THE ACTION OF CORTISONE ON EXPERIMENTAL ACUTE ROENTGEN DERMATITIS

by

A. H. E. Marshall

It has long been recognized that the sensitivity of cells to ionizing radiation is in part dependent on their proliferation rate and metabolic activity. The depressant effects of cortisone on the proliferation of connective tissue are well known and it has been claimed by GREEN and GHADIALLY (1) that cortisone also inhibits cell division in the normal epidermis. Such effects might be expected to influence the radio-sensitivity of both the epidermis and the underlying dermis. In addition, cortisone has a pronounced general anti-inflammatory action, and might affect the development and course of the actual acute radiation lesion of the skin. The failure of SMITH et al. (2) to influence with cortisone or ACTH the mortality of mice given whole body roentgen radiation, may possibly be due to the lack of inhibition of cell proliferation in the normal bone marrow by either hormone, and by the adverse effects of these substances on the bacterial infection which is a common sequel of whole body irradiation.

Methods. 170 mice of two separate strains were employed in these experiments. Albino mice of a highly inbred strain (St/Eh) were used for radiation of the body skin, and a hairless recessive strain for radiation on the tail. Mice for body radiation were secured singly to a board, without anaesthesia, their fur clipped, and were radiated on a 1 cm diameter field on the hip region by contact therapy. Mice for tail radiation were placed in lead lined boxes, their tails led through holes and secured in a 2 cm diameter field in contact with the roentgen applicator. A single air dose of 3,500 r was used for body exposures and of 4,000 r for tail exposures. This dosage is sufficient in mice to produce severe

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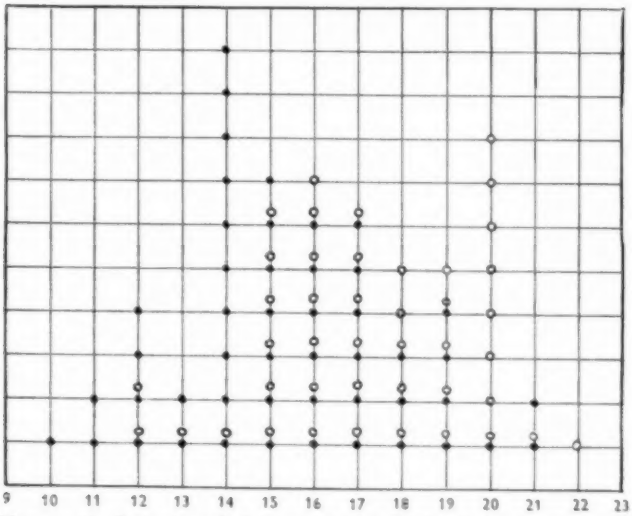

Diagram 1. Latent period to onset of radiation lesion in 48 normal mice (●) and 43 mice treated with cortisone (○) from 1 day before radiation to 3—6 days after radiation.

moist epidermitis and occasional ulceration. Signs of generalized radiation damage (petechiae and pallor of skin) were observed in only two animals of the total radiated. Mice of 3 months of age were employed in the majority of the experiments.

Age differences below 3 months were equalized in treated and control groups of animals. No animal less than 70 days old was employed. Female mice were principally used owing to the tendency of male animals to fight and damage radiated areas of skin. Radiation factors used were — Siemens "Monopan", 60 KV, 4 Ma, 3 cm distance H. V. L. — 2.8 mm Al., output 408 r per minute. Cortisone acetate (Ciba or Merck) was injected under two schedules of dosage. In the first series of experiments a dose of 0.25 mgm was given 24 hours before radiation, 0.5 mgm 4 hours before radiation, and 0.25 mgm daily for 3 to 6 days after radiation. In the second series, a dose of 0.25 mgm was given daily from the 7th day after radiation and until 10 days after lesions had developed on all the treated animals in each experiment. Control animals received an equivalent volume of normal saline. Records were taken in control and treated animals of the latent period from radiation to the earliest onset of the skin lesion, of the degree of intensity of the lesion and the

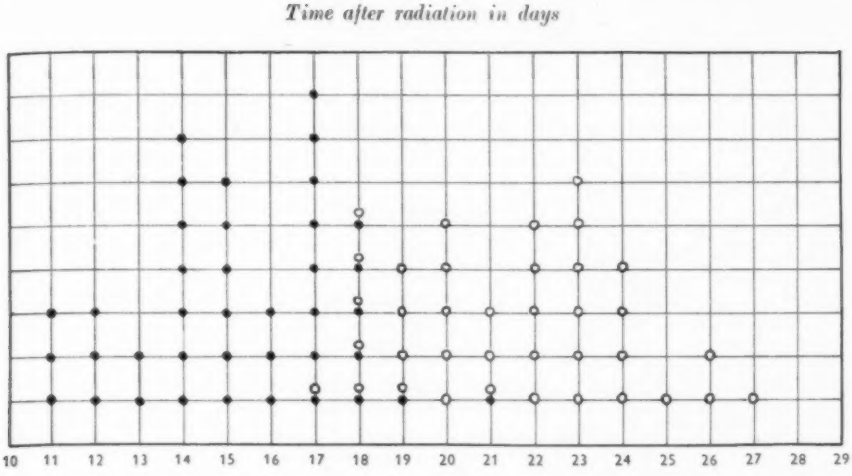

Diagram 2. Latent period to onset of radiation lesion in 39 normal mice (●) and 37 mice receiving cortisone (○) from the 7th day after radiation.

presence or absence of ulceration, and in mice radiated on the body, of the diameter of the area of depilation. The animals were killed at periods of from 10 to 30 days after all had developed lesions and the radiated areas removed for histologic examination.

The area of depilation was expressed as the product of two diameters; the area was measured in all cases at an interval of 10 days after the last animal in each group of four had shown the earliest sign of a lesion.

Results. The results are shown in diagrams 1—3. In diagrams 1 there is a significant increase in the latent period of onset of the lesion in mice treated with cortisone from 1 day before to 6 days after radiation. Average latent period (control): 15.55 days, average latent period (treated): 17.28 days. Control S.D. = 2.91, treated S.D. = 3.18. St.e. (control) = 0.42. St.e. (treated) = 0.485, t = 2.88. In diagram 2 there is a similar but greater increase in the latent period of onset in mice treated with cortisone from the seventh day after radiation. (Average latent period (control) = 15.31 days, average latent period (treated) = 21.41 days. St.e. (treated) = 0.491, t = 8.79.) Diagram 3 shows the significant decrease in the size of the areas of depilation in mice treated with cortisone from the seventh day after radiation. (Control S.D. = 11.17, St.e. = 2.192, treated S.D. = 6.41, St.e. = 1.308, t = 5.76.)

The naked eye appearance of the lesion under cortisone treatment was also considerably modified, the oedema, erythema and oozing of

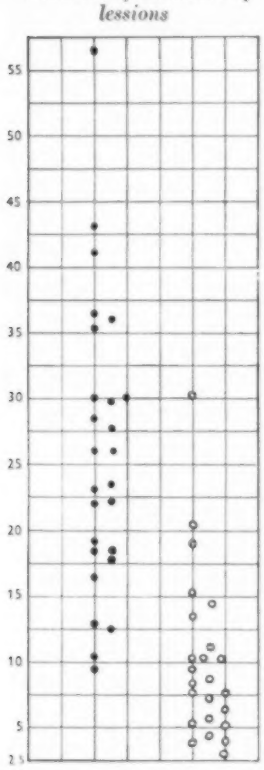

Diagram 3. Variation in size of depilated areas in 26 normal mice (●) radiated on the hip region and 24 mice (○) treated with cortisone from the 7th day after radiation.

serum from the skin surface, seen in the normal animal, being absent or diminished, and replaced by a relatively silent and less acute process. Healing of the damaged skin area appeared to proceed normally under cortisone treatment. The scarring and resultant contracture of the lesion seen in untreated animals did not occur, and a marked diminution of the degree of fibrosis in the dermis was observed microscopically.

Ulceration of the epidermis and underlying dermis, which showed no evidence of healing on microscopical examination, developed in 7 of the 26 control mice (diagram 3) but did not occur in any cortisone treated animal. No recrudescence of the skin damage occurred in the treated animals after withdrawal of cortisone, though an increase in the area of depilation did occur in some mice. In 3 cortisone treated animals, however, a regrowth of hair in the radiated area had commenced in 30 days after the onset of the lesions.

These results indicate that cortisone considerably delays the onset of acute radiodermatitis and restricts the area of damage produced when measured in a given period from its onset. The effect is greatest when the cortisone treatment is commenced shortly before the appearance of the skin lesion and continued throughout its course. This action may be the consequence either of a true protection of the cells in the radiated area and therefore of a lower cellular mortality, or may result from a spreading of the total damage over a considerably longer period and possibly of permitting a certain amount of healing to occur during that period. The latter process would not constitute protection from radiation in a strict sense though it might provide benefit in clinical radiotherapy. The clinical value of an effect in depressing the radiosensitivity of normal tissues is in any event dependent on the absence of a similar action on tumours, and the action of cortisone in this respect calls for further investigation.

I am indebted to Professor J. Engelbreth-Holm for providing the facilities for this work and for much help and encouragement, to Dr. Jens Nielsen for providing facilities at the Radium Hospital, Copenhagen, and to Dr. S. Iversen for assistance in statistical problems.

This investigation was carried out while in receipt of a travelling Fellowship from the London Hospital.

SUMMARY

The administration of cortisone to mice radiated on the skin of the flank or tail produces a prolongation of the latent period before the onset of the lesion and an apparent suppression of its severity. The significance of this finding is discussed.

ZUSAMMENFASSUNG

Gibt man Mäusen, deren Flanken- oder Schwanzhaut röntgenbestrahlt worden ist, Cortison, so erhält man eine Verlängerung der Latenzperiode vor dem Auftreten von Krankheitserscheinungen sowie eine deutliche Herabsetzung der Schwere der Symptome. Die Bedeutung dieses Befundes wird diskutiert.

RÉSUMÉ

L'administration de cortisone à des souris dont on irradie la peau du flanc ou de la queue prolonge la période de latence avant le début des lésions et supprime apparemment leur gravité.

L'auteur étudie la signification de ce résultat.

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FROM THE RADIOTHERAPY DEPARTMENT, UNIVERSITY HOSPITAL, UPPSALA, SWEDEN

SURVIVAL RATE CALCULATION

by

Bengt A. Nohrman

The usual method of evaluating various forms of treatment in medical work, is to compare the survival rate in different series of cases. As regards the mathematical procedure, there are two possible ways of calculating the percentage of survivals. The first is to express the number of survivals after n years directly as a percentage of the number of cases observed during n years — this way of calculation will in what follows be named 'the direct' method. The second method (in this paper called 'the indirect') is to calculate the percentage of survivals on the basis of the mortality rate for each year. When applied to a material in which all cases were observed during n years, both methods yield identical results for the percentage of survivals after any period of observation, not exceeding n years; under such conditions the direct method might be preferred as being less complicated.

If, however, the material is composed in such a way that the entire material was observed during n years, a smaller part of it during $(n + 1)$ years, a still smaller part during $(n + 2)$ years, and so on with a decreasing number of observations for each year, the two methods yield different results. This depends upon the fact that, when using the direct method in such a material, an increasingly greater proportion of the material given must be omitted for each year; hence the survival rate is not calculated in the entire material but in an increasingly smaller fraction of it.

On the other hand, the indirect method makes it possible also to utilize the entire material in a series with a decreasing number of observations for each year as it is founded on the annual mortality, *i. e.* the proportion between the number of deaths during each year of observation and the number of cases exposed to the risk of dying during the same year. This method also offers the means of introducing into the

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calculation a correction for deaths from intercurrent diseases, which might be suitable in studying the survival rate, for example, in cancer in different ages; with rising age the intercurrent diseases play an increasing rôle in the cause of death (NOHRMAN 1949).

When using the indirect method, the mortality (Q) for each year of observation must first be calculated from the formula

$$Q = \frac{d}{d + l} \quad \text{..... (formula 1)}$$

in which

d = the no. of deaths during the year in question,
l = the no. of survivals at the end of the same year.

The percentage of survivals is then

after 1 year $= 100\ (1 - Q_1)$
» 2 years $= 100\ (1 - Q_1)\ (1 - Q_2)$
» » » $= 100\ (1 - Q_1)\ (1 - Q_2) \ldots\ldots\ldots (1 - Q_n) \ldots\ldots$ (formula 2)

where the index marks the year of observation.

Formula 1 might also be given the form

$$(1 - Q) = \frac{l}{d + l}$$

from which the expression $(1 - Q)$ may thus be directly obtained.

As pointed out above, it might be desired, when studying a series of cancer cases, to introduce a correction for deaths due to diseases other than cancer. Assuming the patients who died of an intercurrent disease to have been exposed to the risk of death from cancer during half the year in which they died, the cancer mortality (q) is for each year

$$q = \frac{c}{\frac{i}{2} + c + l} \quad \text{..... (formula 3)}$$

in which

c = the no. of deaths from cancer during the year in question,
i = the no. of deaths from intercurrent diseases during the same year,
l = the no. of survivals at the end of the same year.

The figures thus obtained for q are then inserted in formula 2 in place of Q.

In table 1 a survey is given of a series of cases, all of which underwent radical mastectomy during the period 1. 1. 1936 to 31. 12. 1941 inclusive (NOHRMAN 1949). Each case was observed at least until 1. 1. 1947, thus making it possible to calculate the five year survival rate,

Table 1

Number of cases treated each year: number of survivals 1. 1. 1943 (above the double line) and 1. 1. 1947 (the entire table)

Year of treatment	Number treated	Number of survivals after				
		1	2	3	4	5 yrs
1936.....	58	49	32	26	23	19
1937.....	66	57	41	30	24	22
1938.....	76	66	53	43	37	33
1939.....	85	74	64	54	45	42
1940.....	86	77	63	55	48	41
1941.....	102	95	70	52	42	37
	473	418	323	260	219	194

based on direct observations. In order to illustrate the two methods of calculation, this series is assumed to have been observed only until 1. 1. 1943 which implies that in table 1 only the figures above the double line are supposed to be available for the calculation.

The survival rate in a material of this type where the number of observations decreases with each year, must be calculated on the annual mortality, *i. e.* according to the indirect method. Using the direct method under these circumstances implies, as mentioned above, that an increasing part of the material must be omitted for each year of observation; in the example chosen (table 1, above the double line), the five year survival rate can be directly calculated only on the 124 cases observed during five years, thus omitting from the calculation nearly 3/4 of the material given. Calculation according to the indirect method utilizes the entire material in a far better way.

In order to facilitate this calculation the part of table 1, which is above the double line, should be written:

Table 2

The same material as table 1, above the double lines: the number of survivals and of deaths up to 1. 1. 1943

	Year of observation				
	1.	2.	3.	4.	5.
No. of survivals at end of year	418	253	153	84	41
No. of deaths during year	55	70	37	15	6

The five year survival rate having been calculated with both methods, the figures obtained were compared with the percentage actually alive, *i. e.* when the figures below the double line in table 1 also were available. The results are given below:

Direct method	33.1 %
Indirect method	41.3 %
Actually alive	41.0 %

The figures obtained by the indirect method coincide much better with the percentage actually alive, than those given by the direct method of calculation.

The necessity of omitting a part of the material when calculating the percentage of survivals with the direct method in a series with a decreasing number of observations for each year may lead to absurd consequences. The following example, taken from the author's previous paper on breast cancer, refers to the cases which underwent only amputation of the breast. It should be noticed that the percentage of survivals remains the same even in a larger material, only the proportions are unchanged between the number of survivals and the number of deaths.

Table 3

Example of calculation

	Year of observation					
	5.	6.	7.	8.	9.	10.
No. of cases treated	43	38	33	25	16	11
No. of survivals at end of year	25	19	16	14	6	5
No. of deaths during year	(1)	3	1	0	0	0
Percentage of survivals with						
direct method	58	50	48	56	37	45
indirect method	58	50	47	47	47	47

As is seen from the upper half of the table not a single death occurred during the three last years of observation. Nevertheless the percentage of survivals calculated with the direct method varies for these years between 37 and 56, and is higher after 10 years than after 9. The indirect method gives the correct results: if no death occurs, the percentage of survivals must remain unchanged.

SUMMARY

In a material in which all cases are observed over *n* years the percentage of survivals may be calculated directly as 100 times the quotient between the number alive after *n* years and the total number of cases in the series. Under the same circumstances the calculation may also be performed on the basis of the annual mortality, this calculation being, however, a little more complicated. The latter method must be used in handling a material with a decreasing number of observations for each year, and also offers the means of introducing a correction for intercurrent deaths.

ZUSAMMENFASSUNG

In einem Material, in dem alle Fälle *n* Jahre beobachtet geworden sind, kann man die Prozentzahl der Überlebenden unmittelbar als 100 Male den Quotienten aus der Zahl der Überlebenden nach *n* Jahren und der Gesamtzahl der Fälle in der Serie berechnen. Die gleiche Berechnung kann auch auf der Basis der jährlichen Mortalität in der Serie geschehen; die Methode ist jedoch komplizierter. Die letztere Berechnungsmethode muss benutzt werden, wenn man ein Material mit von Jahr zu Jahr sinkender Anzahl von Fällen bearbeitet; sie ermöglicht es auch, eine Korrektion für interkurrente Todesfälle einzuführen.

RÉSUMÉ

Dans une série de cas tous suivis pendant *n* années on peut calculer le pourcentage des survies au bout de *n* années directement comme 100 fois le quotient du nombre des survivants par le nombre total des cas de la série. On peut aussi, dans les mêmes conditions, faire ce calcul sur la base de la mortalité annuelle dans la série. C'est cette méthode qu'il faut utiliser pour juger une série dont le nombre des cas diminue chaque année; elle permet en outre d'introduire une correction pour les morts par maladie intercurrente.

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FROM THE GYNAECOLOGICAL DEPARTMENT (DIRECTOR: GUNNAR GORTON),
KING GUSTAF V JUBILEE CLINIC, LUND, SWEDEN

PLASMACYTOMA OF THE VAGINA

Case Report

by

Gustaf Appelberg

Tumors composed of plasma cells are, as a rule, localized to the bone-marrow. Extra-medullary plasma cell tumours, of which the great majority are encountered in the upper respiratory passages (GORMSEN 1942, HELLWIG 1943), are definitely more rare and a plasmacytoma of the female genital tract is an extremely rare finding. A case of plasmacytoma of the vagina, treated in the Jubilee Clinic in Lund in 1951, therefore merits publication.

The patient was a woman aged 74 years. Para 9. Two daughters died from cancer of the womb. No miscarriages. Menarche at the age of 18. Menstruation 4—5/28 days. Menopause at the age of 37. For the previous year, blood-stained discharge from the vagina. On account of this, she came for consultation in the Jubilee Clinic on 8. 3. 1951. General condition: nothing of note. No infiltration of the skin. No palpable glands in the groins, axillae or neck. Liver and spleen on palpation not enlarged. Gynaecologic examination: Immediately above the vaginal introitus over the urethral prominence and in the urethral sulci a cushion-like swelling was encountered. This was raised 2—3 mm above the mucous membrane and was approximately 1 cm in breadth from below upwards. A resistance was noted in the posterior wall of the vagina. Above these, the vagina narrowed into a funnel shape. Low, soft portio with obliterated fornices. Body of the uterus retroflexed, small, firm, mobile and smooth. Parametria: no abnormality. No pathologic resistances palpable in the surrounding tissues. Examination with speculum: Posterior and anterior vaginal mucous membrane, corresponding to the cushion-like thickening, presented a gelatinous appearance of bluish discoloration. Provisional diagnosis: Leukaemic infiltration. The report on the biopsy from this region read (P. A. D. No. 2874/51): In the biopsy fragments from the vaginal tumour particularly cellular tumour tissue is seen which is diffusely demarcated at the periphery. On the surface, however, the squamous epithelium is preserved and completely regular. The tumour tissue is composed of plasma cells of various degrees of maturity, from completely typical mature plasma cells to immature elements resembling reticular cells. Among these latter a number of mitoses

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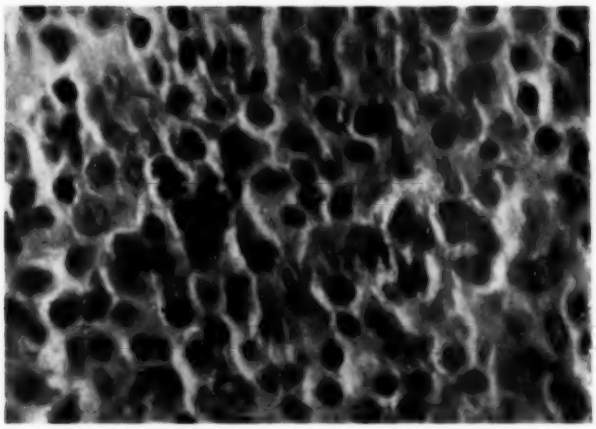

Fig. 1.

are seen. Further, moderate admixing of lymphocytes and polymorphonuclear leucocytes is seen. Diagnosis: Plasmacytoma of the mucous membrane. The diffuse demarcation at the periphery and the appearance of the cell picture and the occurrence of mitoses favour the supposition of the process being malignant. (BERG.) Fig. 1.

Prior to radiologic treatment, a further biopsy from the same region was performed under local anaesthesia which showed in principle the same picture as previously. (MELLGREN.)

30. 3. 1951 — sternal puncture (P. A. D. No. 3324/51): Moderately cellular smear. The cell picture shows a normal appearance. Cell counts do not demonstrate any increase in the number of plasma cells and the picture does not support the diagnosis of myeloma. (LINELL.)

31. 3. 1951 — Roentgen examination of the long bones together with the lumbar spine and pelvis showed no pathologic changes. 2. 4. 1951 — radium treatment of the vagina (1,400 mg/hours) and teleradium treatment focussed on the vulva (1,200 r). The patient was discharged but readmitted on 22. 4. 1951 for further treatment. She had been free from symptoms while at home. Further biopsy (P. A. D. No. 4329/51): The biopsy specimen from the vagina is covered by layers of squamous epithelium, which is partly ulcerated. The underlying tissue is fibrous and infiltrated by thin strands of plasma cells. Unacquainted with previous investigations, one might now have interpreted the picture as that of chronic inflammation. (AHLSTRÖM.)

23. 4. 1951 — radium treatment of the vagina (1,400 mg/hours). On discharge on 24. 4. 1951 gynaecologic examination still showed a number of elongated areas of gelatinous appearance.

Blood examinations: 15. 3. 1951. R. B. C. 3.28 mill. Hb. 67 %. W. B. C. 3,000. Differential count: neutrophils 60, eosinophils 4, basophils 0, lymphocytes 32, monocytes 2. B. S. R. 35 mm. W. R.: negative. 29. 3. 1951. R. B. C. 3.38 mill. Hb. 70 %. W. B. C. 3,400. Differential count: neutrophils 50, eosinophils 3, basophils 0, lymphocytes 47, monocytes 0. B. S. R. 55 mm. Total protein in serum 6.6 %, consisting of albumen 4 % and globulin 2.6 %.

23. 4. 1951. R. B. C. 3.4 mill. Hb. 67 %. W. B. C. 3,600. Differential count: neutrophils 71, eosinophils 1, basophils 0, lymphocytes 28, monocytes 0. B. S. R. 90 mm. Urine: sugar (ALMÉN): negative, albumen: negative, BENCE-JONES protein: negative.

Follow-up examination 24. 5. 1951. Subjectively: symptom-free. Objectively: Normal vagina. Sign-free. Continued control examinations, the last being on 27. 5. 1952, showed status quo. B. S. R. still rather high, 46 mm.

Discussion

The account concerns a rare case of plasmacytoma situated in the vagina. Sternal puncture showed a normal picture with no signs of myeloma. Roentgen examination of the long bones and the pelvis show no signs of any generalized process. The albumen-globulin ratio did not deviate from normal. The B. S. R. was, however, rather high in contrast to statements (BING 1940, GORMSEN 1942, RINGERTZ 1938) according to which the B. S. R. in extra-medullary plasmacytoma is, in general, normal but greatly increased when metastases in the bone-marrow are present. Histologically the tumour showed signs of malignancy, but proved sensitive to radiation in so far as it was possible to ascertain a certain effect attributable to treatment on comparing the histologic picture at the third biopsy with the two previously obtained. The tumour was treated radiologically and the patient was at follow-up examination, over 14 months later, free from signs and symptoms. The period of observation is, however, short, particularly if the information given in the literature (JAEGER 1942, HELLWIG 1943), according to which extra-medullary plasmacytomata may metastasize after a latent period of up to 15 years, be taken into account.

SUMMARY

The author describes a case of plasmacytoma of the vagina. Sternal puncture showed a normal picture with no signs of myeloma. Roentgen examination of the long bones and pelvis showed no structural changes. The albumen-globulin ratio was normal. The tumour, which histologically showed signs of malignancy, was treated radiologically and the patient was at follow-up examination, over 14 months later, free from signs.

ZUSAMMENFASSUNG

Der Verf. beschreibt einen Fall von Plasmozytom der Vagina. Die Sternalpunktion zeigte ein normales Bild ohne Anzeichen für ein Myelom. Die Röntgenuntersuchung der langen Röhrenknochen und des Beckens zeigte keine Strukturveränderungen. Das Globulin-Albuminverhältnis war normal. Der Tumor, welcher histologisch malign war, wurde radiologisch behandelt und der Patient war bei der Nachuntersuchung, mehr als 14 Monate später, symptomfrei.

RÉSUMÉ

L'auteur présente un cas de plasmocytome du vagin. La ponction sternale a montré une formule normale sans signes de myélome. L'examen radiologique des os longs et du

bassin n'a pas mis en évidence de modifications de structure. Le rapport sérine sur globuline était normal. La tumeur qui présentait des signes histologiques de malignité fut traitée par radiothérapie et la malade n'avait aucun symptôme à un examen de contrôle, plus de 14 mois plus tard.

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BOOK REVIEWS

La Tomographie de la Base du Crâne en Neurochirurgie et Neuroophtalmologie par H. Fischgold, M. David et P. Brégeat. 138 pp. 107 ill. Masson & Cie. Editeurs, Paris. 4e trim. 1952.

In this work, the Paris radiologist Fishgold together with a number of assistants discuss the value of tomography in the roentgen examination of the base of skull. The text is brief and concise and the cases described are presented with drawings and original films in a readily accessible manner. The value of tomography in the study of the walls of the orbit, the olfactory region and the sphenoid bone in cases of tumours and aneurysms is pointed out. One chapter deals with the anatomic analysis of the sella turcica in different types of deformity and destruction. Another chapter contains an interesting account of the importance of tomography in the comparison of the size and wall thickness of the right and left middle fossae in cases of unilateral atrophy of the brain. Occipitocervical anomalies as well as basilar impression are analysed in an elegant manner with the help of tomography.

This important work may be said to give in the form of a manual a description of the roentgenologic changes in the base of the skull in various intracranial diseases and at the same time to show in a convincing way the significance of tomography in detailed anatomic analysis.

Folke Knutsson.

Selected Papers from the Royal Cancer Hospital and The Chester Beatty Research Institute, London. Vol. VI. 1948—1949. 604 pp.

In this volume the reader is given a good survey of the achievements in the radiotherapy, radiophysics, radiobiology, biochemistry and chemotherapy of cancer attained in a cancer hospital. The description of the 30 million volt synchrotron devoted to medical research is especially worth mentioning. Reports of important studies on the radiobiologic effects of roentgen rays in the 30 MeV region will certainly appear in the future. The low output constitutes a heavy drawback as concerns cancer therapy, although the experiences gained are extremely valuable for future development. The distribution of energy absorption in the body depends very much on the precise geometry employed and at the lower energies the problem becomes more complex.

A report is also given on a ten gramme teleradium installation. The mean radium—skin distance has been fixed at approximately 8.3 cm. The indications for treatment should be the same with the new apparatus as with the five gramme unit previously employed.

Smithers gives a survey of bone changes following irradiation. He has also investigated the family histories of 459 patients with cancer of the breast. A significantly high death-rate from cancer of the breast was observed in families of patients with that disease but no higher death-rate from other forms of cancer than would be expected in the general population.

The now well-known intracavitary irradiation of certain bladder tumours by radioactive isotope solutions is described. The question of dosage remains still unsolved. Treatment should probably be given fractionally in order to avoid heavy reactions of the normal bladder wall.

One is used to reading individual case histories of occupational cutaneous cancer attributable to certain chemicals in industry but Henry has collected a great number of such cases. From the technical view-point of protection, this part is particularly interesting.

Folke Jacobsson.

DIE ZEREBRALE ANGIOGRAPHIE. Von H. Krayenbühl & H. R. Richter. 213 Seiten, 100 Abb. Georg Thieme Verlag, Stuttgart 1952. DM 59.70.

After a short but fairly complete review of the literature the technique of cerebral angiography is dealt with. The puncture of the carotid artery is described in detail. The different methods of vertebral angiography are shortly discussed. Percutaneous puncture of the vertebral artery is performed lateral to the carotid artery, which in my opinion is a less reliable method than the one in which the needle is introduced medial to the artery and directed laterally. The anatomy of the vessels is clearly described from a practical point of view. The authors' statement that the capillary phase is of no importance for the angiographic interpretation is, however, surprising. In my experience this phase, in many cases, affords the best possibilities for localizing a tumour as well as for determining its extent and true nature. The indications for angiography and the risks involved with the method are dealt with in a special chapter. The authors' declaration that angiography should practically never have any influence on cerebral pressure and oedema cannot in my opinion be true. The effect of breaking the blood-brain barrier, as demonstrated by OLSSON and BROMAN (and accepted by the authors), should in my opinion be an increased outflow of fluid to the brain tissue. The authors probably intend to say that the risks of the occurrence of 'coning', which sometimes happens after ventriculography, is minimal. Vascular diseases (malformations, haematomas and occlusions of the arteries) are shortly described. In the topographic description of the tumours the authors succeed, generally speaking, in grouping the tumours in a way, which fulfils requirements from anatomic and angiographic as well as clinical points of view. In the description of the vascular displacement of the different groups, the typical appearances seen in the a. p. film are, in my opinion, not sufficiently considered. The authors seem on the whole to rely more on stereoscopic lateral than on a. p. views. This is evident also from the illustrations, where only a few a. p. films are included. Otherwise the illustrations are most informative and, from a technical point of view, excellent; most of them are brought together at the end of the book in a special atlas. Short clinical notes and drawings are in most cases added. The displacement of the veins in cases of central tumours is more completely described than in any other publication I have hitherto seen. The bibliography is extensive and fairly complete. There is also a useful subject index at the end of the book.

The work can be recommended as an introduction in the field of cerebral angiography. It also provides, however, valuable information to the more experienced neuroradiologist.

I. Wickbom.